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# ARCHIVES OF DISEASE IN CHILDHOOD

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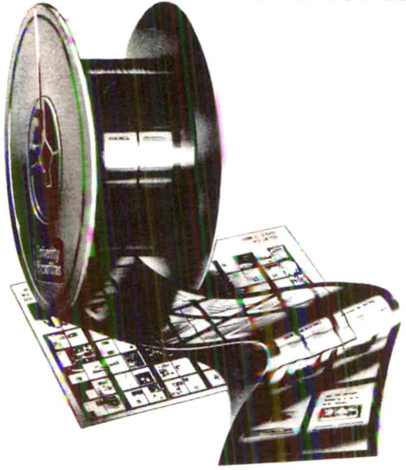

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*Archives of Disease in Childhood,* 1987, **62,** 653–655

## *Annotations*

# Doctors and nurses in neonatal intensive care: towards integration

Much of the current debate about neonatal intensive care services centres on the broader aspects of organisation at national and regional level. Yet the real organisational challenge lies at the point of delivery of the service—in the neonatal intensive care unit itself—where the demand created by an increasing number of ill preterm babies exceeds the available number of doctors and nurses.

The medical staffing problem at junior level arises from a conflict between the service needs of patients, and the need to protect the career structure of junior doctors. Put simply, if intensive care cots are to be adequately staffed at junior level this would require additional junior staff, in excess of the numbers needed to be trained to fill predicted vacancies for consultant paediatric posts. Implicit in this is the idea that the primary function of junior doctors is to receive training, and that their role in the provision of a service to patients is of secondary importance.

The concept of a neonatal intensive care unit, in which consultants are committed to cot side care, certainly needs to be explored. The nature of neonatal intensive care is such that most consultant paediatricians with responsibilities in this field already spend a substantial proportion of their time directly involved with delivery of the service to the patient in terms of examination, diagnosis, and treatment. An even greater participation in dedicated cot side care, such as carrying out practical procedures, poses the question, 'which other components of the consultant's work might need to be sacrificed?'

Consultants have a continuing responsibility for their patients, a privilege which most of them would be reluctant to forego. Any rota arrangement made with a colleague is for personal convenience, and this temporary cover does not negate a consultant's duty to his or her patient. Thus parents identify the consultant as being ultimately responsible for the care of their baby, and also it is the consultant who is in a good position to discuss with parents in a consistent way the varied and often complex aspects of their baby's present and future health. In most cases continuity extends to the outpatient clinic after the baby is discharged. A radical change in the work pattern of consultants on neonatal intensive care units would have to be based on a formal rota or shift system—at the expense of this continuity of personal care and responsibility. This cannot be in the best interests of patients and their parents, nor is it the most cost effective use of a consultant who spends a minimum of 15 years in undergraduate and postgraduate training before being appointed.

The basis of neonatal nursing staff shortages is different. Some neonatal intensive care units do not even have a numerically defined establishment of nursing staff. Financial restraint does play an important part in limiting the numbers of neonatal nurses but it is not the only problem. Many neonatal intensive care units, even some traditionally prestigious ones, are experiencing problems in recruiting nurses, and many nurses leave within a short time of being appointed. Poor job satisfaction, lack of a creative role in their work, physical and emotional pressures of neonatal intensive care, and poor salary all contribute to this. Moreover, there is a shortage of trained neonatal nurses from which to draw (see page 760).

We have reached a cross road with respect to staffing of neonatal intensive care units, and perhaps now is the time to reflect whether traditional work patterns could be modified. The nature of the clinical work on neonatal intensive care units falls into different but overlapping categories: diagnosis and treatments including the prescription of drugs; monitoring and observations; responding to emergencies; practical procedures; conventional nursing hygiene care; and attending to the very legitimate needs of parents.

Can we conceive a strategy that would permit a better integration of nursing and medical care for the benefit of babies, and which would at the same time make the work of neonatal nurses more creative, and perhaps encourage recruitment to the specialty? There is a danger in viewing this solely in terms of an extended role towards carrying out practical procedures, currently the responsibility of doctors. Although this might satisfy some nurses who are gifted in this field, it might tend to encourage the separate growth of nurse technicians and 'task orientation', which creates further polarisation and is contrary to the principle of integration.

A key factor which distinguishes the work pattern of the nurse and the doctor at the point of delivery of the service is that the nurse is in constant contact with the baby when she is exposed to rapidly evolving clinical situations. The late recognition of warning signs in babies can lead to a relentless cascade of disturbed physiology, culminating in a downward spiral of clinical deterioration, with potential long term neurodevelopmental and other health implications for surviving babies. Neonatal nurses already use their skills to recognise deviations from the norm in respect of the observations they make. Yet there is a paradox, in as much as the growth of electronic monitoring of vital signs and blood gases carries the risk of divorcing nurses (and doctors) from the totality of a baby's medical needs. Indeed, nurses in some busy units already comment that under the pressure of staff shortages 'hourly observations' devolve into a boring ritual of transferring electronic readings into the nursing records. What is recorded on the chart might not give any 'feel' about the baby's true progress.

The fact of staff shortages is so entrenched that it could habitually dictate an unfavourable work style for neonatal nurses for the future, thus continuing the cycle of poor incentive and poor recruitment. That is why we should not let current staff shortages deter us from exploring the idea of better integration of the skills of the nurse and doctor. The cot side devotion of neonatal nurses provides an opportunity for them to extend their clinical skills as diagnosticians—inferring from events and clinical assessment the nature or cause of particular situations—before the baby enters that downward spiral of deterioration. Against this solid background those who wished to could, with appropriate training, build on this and carry out procedures such as putting babies on ventilators, sampling and measuring arterial blood gases, adjusting ventilator settings, inserting peripheral lines and arterial catheters, draining pneumothoraces, and treating hypovolaemic shock.

Even where a regional neonatal intensive care referral service operates, the district special care baby units cannot ignore their responsibilities for their sick babies, nor would they wish to. These units are increasingly called on to provide a service, including monitoring of unstable babies and vigilance for complications, which is beyond that enshrined in the expression 'special care'. Many of these units also provide mechanical ventilation, sometimes beyond 24 hours, until a place can be found for a baby in a referral unit. This situation will not go away; nor is it likely that the present constraints on the creation of new posts at senior house officer and registrar grades will be lifted to meet the needs of these babies, who, in many cases, are not receiving the care they deserve. The provision of appropriately trained neonatal nurses in sufficient numbers working with the registrar and consultants in district special care baby units would help to alleviate this problem. There is no reason why the job content of junior medical staff would be weakened; on the contrary, it would certainly enhance training opportunities for senior house officers in district hospitals. In the regional centres they would still retain a large role in neonatal care, only sharing their responsibilities with neonatal nurses.

It is appreciated that not all nurses working in neonatal intensive care have long term career motivations in this specialty. Those who do would, after training, contribute to a core of such nurses in district hospitals and regional centres. Thus integration would improve services for the newborn and at the same time provide a real opportunity for certain nurses to pursue a career in neonatal medicine in a way that promoted job satisfaction. It is essential that nurses and doctors each know where their responsibilities lie because this helps to secure the safety of patients. An integrated work pattern raises the issue of the extent to which neonatal nurses can be regarded as autonomous decision makers. A major change would be required to change the fundamental precepts that govern the regulations for the prescription of drugs. The wellbeing of ill newborn babies, however, depends far more on factors other than the medicines they are prescribed.

Those debating autonomy should not be shy of allowing undercurrents to surface, because it is only by frank discussion that the nursing and medical professions learn to respect each other's anxieties. Doctors do pose a threat to some nurses. It is easy to understand the potential conflicts which exist at present when experienced neonatal nurses work alongside less experienced senior house officers, who rotate through the unit every six months or less, and who, none the less, are responsible for prescribing a wide range of treatments, albeit under consultant supervision. The fact that each patient is admitted under the care of a named consultant who is responsible for directing treatment might also be a source of intimidation for some nurses, but the extent to which this occurs usually reflects the personality and approach of the consultant.

Integration is not about the right to prescribe treatments and the right to be in charge of patients. Instead it is about the degree of responsibility nurses wish to accept and doctors are willing to share. Those who have been appropriately educated and trained and who have proved themselves under supervision, be they doctors or nurses, have earned the right to perform whatever they have been taught to do. None of us is autonomous when it comes to looking after patients, and much can be done to resolve potential conflicts between nurse and doctor in an integrated service. Indeed. forward looking units already operate within a framework that encourages good working relationships.

Firstly, each unit should have a policy which serves as a broad guide for the management of babies with various disorders. This policy, decided jointly by medical and nursing staff, should combine elements of traditional nursing care with medical treatment. It should be the subject of regular formal reviews and revision to take account the pace of change occurring in neonatal practice.

Secondly, it is now common for individual nurses on each shift to identify with particular babies to provide an element of continuity of care throughout the shift; in addition, several experienced neonatal nurses, drawn from the core who have received special training, should work outside the traditional shift system and they, together with medical staff, should provide continuity of care between shifts.

Thirdly, by using their extended clinical skills continuously by the cot side the contribution of nurses to ward rounds is considerably enhanced. Under these circumstances joint ward rounds permit more critical planning of a baby's total needs and are intellectually stimulating and educational for all the staff.

Fourthly, it might be helpful to have joint medical and nursing representation (at an appropriate level) on interview committees for staff appointments to neonatal intensive care units. There is scope for assessing more critically a candidate's potential for work in neonatal intensive care because a nurse or doctor might appear superficially to be suited to an integrated work arrangement and yet might prove to be a burden

Integration cannot be considered without first giving detailed attention to the numbers of nurses required to work such a system and the appropriate mix of learners and experienced staff This will entail research into work load in relation to work patterns, and a review of current nursing and medical procedures because some routines may have developed by habit and are neither efficient, nor of benefit to the baby.

Although it is essential for neonatal units to have their own 'establishment' of nurses, staff levels should emphasise the number of experienced nurses and learners required for duty on each shift in relation to work load at that time. One of the serious management problems posed by neonatal intensive care is the erratic fluctuation in work load. It is unfortunate that at present trained and experienced neonatal nurses who offer themselves for part time work are not always welcomed because of inflexible local policy governing the employment of part timers.

The education and training requirements to meet an integrated service need to be addressed by the appropriate professional nursing organisations. Attendance at a prescribed course of study, such as one of the current English National Board courses on neonatal intensive care, is certainly not the sole requirement. There is, even now, an urgent need to develop a form system of in-service training for neonatal nurses, emphasising cot side teaching. Intensive care units require the services of neonatal nurse teachers, and these posts should be seen as prestigious senior positions The present avenues for promotion in nursing care entail ascending the ladder away from patients, and there is a need to retain trained and experienced sisters where the service is delivered. Their service input to patients should allow them adequate time to give learners the benefit of their experience, and this should be seen as their primary role. These teaching posts could also be used for training midwives on post-natal wards, thus facilitating the practice of special care on the wards and avoiding unnecessary admission of babies to the neonatal medical unit.

Integration must be seen for what it really is—namely, as a genuine desire to bring about better care for sick babies and better job satisfaction for nurses, against the backgrounds of what is potentially a very serious crisis in medical staffing, which other specialties will also have to come to terms with in their own way. It cannot be contemplated without a review of nurse staffing requirements because it would be a retrograde step if it developed at the expense of the many other facets of care that nurses currently provide, including total family care and comforting grieving parents. One attraction of integration is that it provides the proper framework for neonatal nurses to assume a more responsible role, not only with parents, but with key professional groups working in neonatal services, such as social workers, and it also opens up realistic avenues for research by neonatal nurses. The hallmark of innovative management is not to despair in the face of a crisis but to exploit the situation to bring about change.

We are very grateful to Angela Carton, Clinical Nurse Manager, Neonatal Medical Unit, North Western Regional Perinatal Centre, St Mary's Hospital, Manchester, for her helpful comments

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# Is your grommet really necessary?

Otitis media with effusion or glue ear is one of the most common chronic conditions affecting children world wide. Diagnosis is difficult in young children. Diagnostic techniques should include use of pneumatic otoscopy, tympanometry, and pure tone audiometric or other hearing assessments, according to age. The incidence and prevalence of the conditions vary, depending on the technique used. The prevalence, however, decreases as age increases, being high in 1–2 year olds and low in children over the age of 10; the peak seems to be in children aged 1 to 5 years.

The condition can be mild, moderate, or severe. Most mild and many moderate cases resolve spontaneously within weeks or months. Our investigations suggest that up to one third of moderate to severe cases may also resolve if follow up is continued for more than three months. Many, however, run a relapsing and remitting course, which may last for several years.

At present there seems to be no medical treatment that will effect a long term cure. Various operations have been advocated, both to produce a cure and to prevent recurrence. Adenoidectomy alone or in combination with tonsillectomy and insertion of a grommet or ventilation tube are the most frequently advised, though there seems little evidence to support the addition of tonsillectomy with removal of the adenoids. The number of operations being performed for glue ear both in this country and abroad has increased in recent years.[2] At present there is no satisfactory definition of the condition to allow comparative studies of methods of treatment to be made between centres. Most serious investigators, however, require a minimum period of observation of three months, with more than one examination by a qualified pneumatic otoscopist. Tympanometry and pure tone audiometric studies should be used when possible for diagnosis and for assessment during follow up.

Mild, transient forms of the condition with slight hearing loss, especially if unilateral, almost certainly do not require treatment. Moderate forms, especially if bilateral, may affect speech and language development in younger children. Schooling and behaviour are also affected in older children, and if effusions persist for more than three months in association with symptoms intervention is probably required. In such cases the seasonal variation should be considered when treatment is planned. Severe forms of the condition, especially if bilateral, will invariably require treatment. In such cases the mean audiometric hearing thresholds are usually in excess of 30 decibels in each ear. Naturally the state of the tympanic membrane in terms of retraction, scarring, and atelectasis requires consideration.

Most studies reporting treatment by adenoidectomy, adenotonsillectomy, or insertion of grommets have been of unsatisfactory design and have failed to evaluate each procedure in isolation. Often the effects of adenoidectomy and insertion of grommets have not been analysed separately, neither has a control group treated without operation been included. Many studies have been of short duration and have not taken account of seasonal effect on outcome. Our investigations have tried to overcome these defects in study design, and we have sufficient data, including those obtained during follow up for at least three years, for satisfactory postoperative evaluation. Information obtained during follow up for five years is accumulating for sufficient numbers of patients to indicate certain trends. We investigated clearance of effusions by pneumatic otoscopy, changes in results of impedance studies, and hearing gain on pure tone audiometry. After one year there was no significant difference between any of the treatments in isolation, and this effect persisted for at least three years. In the group that received no treatment there was a slow spontaneous resolution of the effusion with a concurrent change in impedance and hearing gain. At three years fluid was still present in 40% of ears and there was a mean hearing loss of 22 decibels, compared with a preoperative threshold of 31 decibels. The addition of tonsillectomy to adenoidectomy seemed not to confer any extra benefit, and there was no significant difference between adenoidectomy alone and insertion of a grommet. To achieve the same effect with a grommet alone, however, reinsertion was required twice as often as when the procedure was combined with adenoidectomy.[3]

## Insertion of grommets

Insertion of a grommet has two clinical indications. Firstly, it may be a short term measure to ventilate the middle ear when there are reversible changes in the middle ear and tympanic membrane. In these cases there is temporary dysfunction of the eustachian tube; this is the case in almost all children suffering from glue ear. Ultimately the child outgrows this underlying dysfunction and the condition resolves. A grommet may, however, need to be reinserted in 30–50% of cases, and in some cases revision is required on three or more occasions The second clinical group have permanent dysfunction of the eustachian tube and irreversible changes of the tympanic membrane, often showing degrees of collapse or atelectasis. In these cases complete resolution is impossible and longer term ventilation is required. The rate of complications in this group both with and without treatment is high. At present there is no method of detecting, either in infancy or at the outset of the condition, which children will fall into this clinical group.

### Short term ventilation

**Advantages.** Short term ventilation results in immediate improvement in hearing and fairly rapid correction of mucosal changes in the middle ear Any subjective pressure effect or feeling of blockage resolves. Tinnitus often disappears, and sometimes dizziness, if present, will be controlled. Behavioural problems often improve, with later obvious improvement in speech, language, and learning. The effects last for six to 12 months. The procedure requires general anaesthesia but not intubation, so the child can be admitted, have the operation and be discharged the same day. There is clearly some cost benefit compared with other surgical procedures that require admission overnight. There may also be additional benefit for those children prone to recurrent acute exacerbations of suppurative otitis media as well as the underlying middle ear effusion. In these the frequency of otitis may be reduced while the grommet remains patent [4]

**Disadvantages.** The patency of a grommet and the period of retention in the tympanic membrane are insufficient to correct the natural history of the disease in at least 30% of children. This is particularly so in younger children, in whom spontaneous resolution may not be expected for several years and the reinsertion rate may be much higher than that in older children. At the outset of treatment it is advisable to inform the parents of the probable need for reinsertion, which will require further anaesthesia.

There are immediate complications from inserting a grommet. A few patients develop otorrhoea, which is usually transitory but in some cases is longstanding and requires treatment A few children develop otalgia. Damage to middle ear structures and even to the inner ear has been reported, either as a result of myringotomy and insertion of the grommet or from the agents used to clean the meatus before surgery In some children secondary otitis media may develop after swimming, but this is rare It is advisable, however, to recommend that children with grommets may continue to swim but should avoid diving or jumping into the water Soapy bath water may be more troublesome than swimming pool water.

Later complications comprise scarring and loss or damage of the middle layer of the tympanic membrane at the site of the grommet Thin triangular segmental defects are often visible after extrusion. Tympanosclerosis to a variable degree may be seen in as many as 40% of cases after one year and in 70% after two years.[5] It is rarely seen in an ear that has not been operated on, and is much less common when myringotomy alone is performed. Tympanosclerosis tends to worsen with time, and our studies suggest that after five years there is a slight but detrimental effect on hearing ability in those patients with the most severe forms of sclerosis when compared with that of the contralateral ear that has not been operated on. This finding is supported by the longer term follow up studies of Gundersen *et al.*[6] In a few cases persistent perforation of the tympanic membrane results There seems little doubt from the studies by Tos *et al* that insertion of a grommet fails to resolve development of attic retraction in cases of glue ear.[7] This suggests that short term ventilation lacks any protective effect on the possibility of cholesteatoma developing in the long term.

### Long term ventilation

The question of longer term ventilation with specially designed tubes in cases of irreversible dysfunction of the eustachian tube and changes in the middle ear requires further study.

### Summary

There is little doubt that surgical treatment is required for many moderate to severe cases of glue ear, particularly if the condition is bilateral, present for more than three months, and associated with considerable subjective hearing loss. Present evidence suggests that the choice rests between insertion of a grommet or ventilation tube and adenoidectomy. We have shown resolution of 40% of effusions assessed one year after removal of the adenoids, and our data at three years show further improvement.[3] There is also evidence that adenoidectomy in cases selected by age and postnasal airway size may produce resolution in as many as 70%.[8] This single procedure is associated with substantial morbidity and mortality and requires an overnight stay in hospital. By contrast, a grommet can be inserted on a day case basis and is accompanied by less risk. If it is used in isolation, however, readmission to hospital for reinsertion will be required in a high proportion of cases. The immediate gain in hearing and subjective benefit from insertion of a grommet is obvious to all clinicians responsible for such children. By contrast, the hearing gain after adenoidectomy is delayed for some weeks. The tympanic membrane changes caused by a grommet may, however, result in some cases in a slight but permanent hearing loss, which does not occur after adenoidectomy.

A compromise regimen for treatment in bilateral cases may be adenoidectomy, after consideration of age and size of postnasal airway, combined with unilateral insertion of a grommet. In this way the longer term benefit of the single procedure of adenoidectomy is combined with the shorter term benefit of hearing gain that results from immediate reventilation of the middle ear. The use of only one grommet reduces the overall complication rate by half. Naturally myringotomy and aspiration of the contralateral effusion without insertion of a grommet would be carried out under the same anaesthetic.

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***Original articles***

# Should we screen for congenital adrenal hyperplasia? A review of 117 cases

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SUMMARY A total of 117 patients with congenital adrenal hyperplasia who were under the care of paediatricians at Birmingham Children's Hospital between 1958 and 1985 were reviewed retrospectively. There were 47 boys (40%) and 70 girls (60%); 30 of the 47 boys (64%) and 38 of the girls (58% of the 66 whose salt state was known) were salt losers. In all salt losers the condition was diagnosed before the age of 6 months, 90% of the diagnoses being made during the first month. The ratio of boys to girls, the distributions of salt losers to non-salt losers, and the age at diagnosis were studied in relation to the year of birth. Early diagnosis was found to be more common in children born after 1970 due partly to the introduction of a method of assaying the concentration of 17α-hydroxyprogesterone in serum, partly to an increase in the number of paediatricians in the West Midlands, and partly to the appointment of a peadiatric endocrinologist. A neonatal screening programme does not seem to be necessary.

Congenital adrenal hyperplasia most commonly results from a deficiency of 21-hydroxylase, an enzyme required for the production of both cortisol and aldosterone. The prevalence varies between 1 in 490 in Alaskan Yuplik Eskimos[1] and 1 in 67 000 in Maryland in the United States.[2] In Western Europe estimates range from 1 in 5000 to 1 in 13 000 in a series of case reports[3–5] and 1 in 5000 to 1 in 18 000 from neonatal screening.[6–8] Up to two thirds of cases are of the salt losing variety,[5 9 10] which usually presents in the neonatal period with symptoms of vomiting, diarrhoea, and failure to thrive; if it is not diagnosed and treated early the infant may die.

In 1981 a committee of experts reported to the Council of Europe and recommended mass screening for this condition as soon as a suitable assay became available.[11] Adrenal hyperplasia due to 21-hydroxylase deficiency is diagnosed when blood concentrations of 71α-hydroxyprogesterone (17-OHP) are grossly raised,[12] and microassays suitable for mass neonatal screening using capillary blood have been reported.[8 13] There is, however, disagreement over the desirability of neonatal screening for this disease, and there is no unified policy [5 6 10 14] Several pilot studies have been undertaken but no consensus has emerged.[6 8 13 15] The purpose of this study was to review retrospectively patients with congenital adrenal hyperplasia under the care of paediatricians at the Children's Hospital, Birmingham, as part of our assessment of the need for a neonatal screening programme in this region.

## Patients

We studied all patients known to have congenital adrenal hyperplasia who were admitted to the Children's Hospital between 1958 and 1985. Information collected included the patient's date of birth, sex, diagnosis (salt losing or non-salt losing), age at diagnosis, presenting features, and relevant family history. Most patients (102; 87%) were from within the West Midlands region. The ethnic origin was not known in all cases, although at least six were from Asian families. These included three genetic boys (all salt losers) with 3β-hydroxysteroid dehydrogenase (3β-HSD) deficiency who presented at birth with severe hypospadias and incomplete masculinisation. Two of these were siblings whose parents were first cousins. There were no other cases of consanguinity. One non-salt losing girl who presented at birth with ambiguous genitalia was diagnosed as having 11β-hydroxylase deficiency. The remaining patients were believed to have 21-hydroxylase deficiency, either on the basis of results of adrenocorticotrophic hormone stimulation tests as described by Galal *et al*[16] or, in more recent cases, because of an increased serum 17-OHP concentration. Classification of salt losers was by both clinical and biochemical evidence of salt loss.

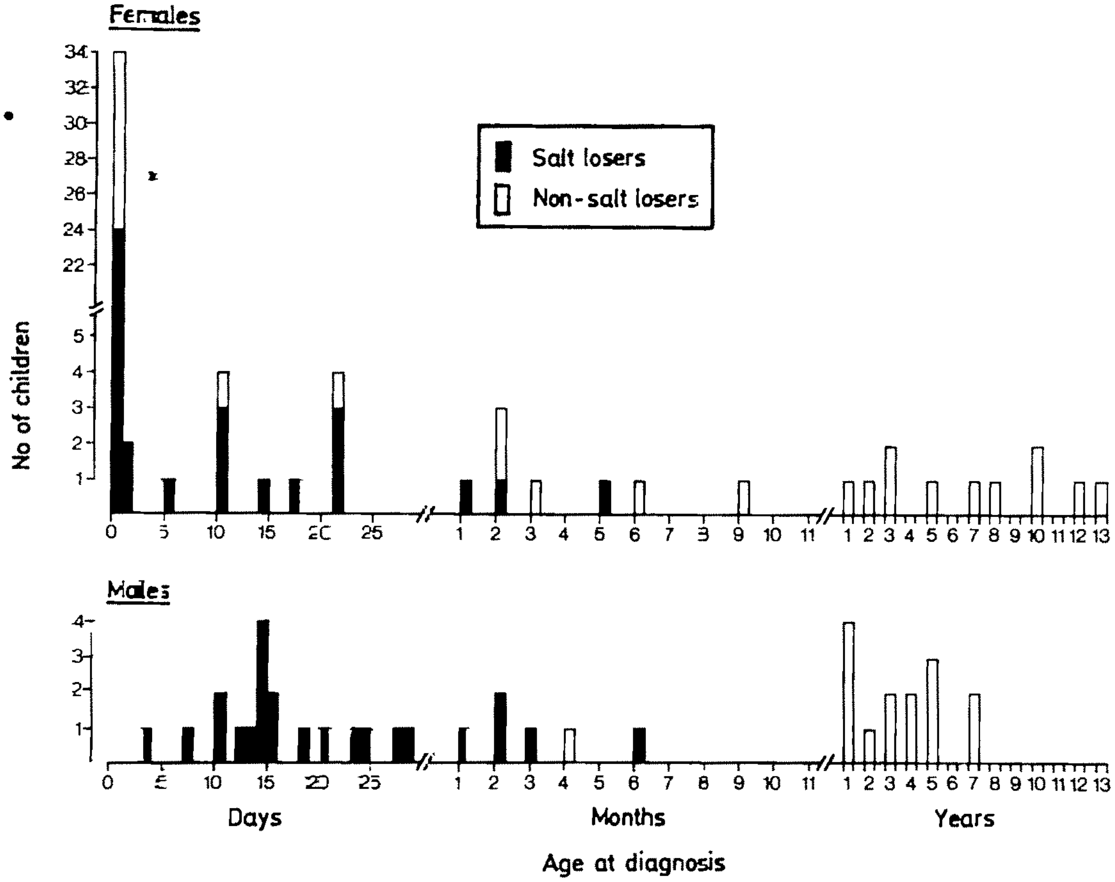

Figure *Age at diagnosis of congenital adrenal hyperplasia*

## Results

We studied 117 patients; in some cases not all the information was available. The patients comprised 47 boys (40%) and 70 girls (60%), the male to female ratio being 2:3. Thirty of the 47 boys (64%) and 38 of 66 girls (58%) were salt losers.

Data from three boys with 3β-HSD deficiency were excluded because they were not comparable with the data from the boys with 21-hydroxylase deficiency. The Figure shows the ages at diagnosis. The condition was diagnosed in half of the girls within 24 hours of birth by the presence of ambiguous external genitalia.

In all salt losers the condition was diagnosed by the age of 6 months, in 90% during the first month.

The age at diagnosis was studied with reference to the year of birth. There seemed to be an improvement in the speed of diagnosis in patients born in the 1970s compared with those born previously. To investigate this we divided the patients into two groups those born before 1970 (group 1) and those born during 1970–85 (group 2). The diagnosis was made earlier in group 2 compared with group 1, as shown by the significantly lower mean age at diagnosis ($p<0{\cdot}01$) and the higher proportion of children in whom the condition was diagnosed by 1 month of age (Table 1) Table 2 shows the distribution of sex and salt loss in the two groups. The

Table 1 *Age at diagnosis related to year of birth*

| | *Born before 1970 (group 1) (n=61)* | *Born during 1970–85 (group 2) (n=46)* |
|---|---|---|
| Mean age (months) at diagnosis | 21 3 | 5 4 |
| No (%) aged less than 1 month | 33 (54) | 34 (74) |
| Boys | 8 (13) | 12 (26) |
| Girls | 25 (41) | 22 (48) |
| No (%) aged less than 1 year | 43 (71) | 39 (85) |
| Boys | 12 (20) | 15 (33) |
| Girls | 31 (51) | 24 (52) |

Table 2 *Proportions of salt losers by sex and year of birth*

| | *All patients* | *Boys* | *Girls* | *Male female ratio* |
|---|---|---|---|---|
| All patients | 68/117* (60) | 33/66 (50) | 35/47 (75) | 1 1 4 |
| Born before 1970 (group 1) | 30/47 (64) | 14/25 (56) | 16/22 (73) | 1 1 1 |
| Born during 1970–85 (group 2) | 38/70* (58) | 19/41 (46) | 19/25 (76) | 1 1 6 |

*Diagnosis was not known in four cases

Table 3 *Presentation of condition in boys and girls (information not available for two salt losers and one non-salt loser)*

| | *Salt losers* | *Non-salt losers* |
|---|---|---|
| *Girls* | | |
| No in group | 38 | 28 |
| No with | | |
| Ambiguous genitalia | 38 | 28 |
| Adrenal crisis or hyponatraemia | 8* | — |
| Vomiting or failure to thrive | 6 | 2* |
| Precocious puberty | — | 6 |
| *Boys* | | |
| No in group | 30 | 17 |
| No with | | |
| Adrenal crisis | 2 | — |
| Hyponatraemia or dehydration | 5 | — |
| Feeding problems or failure to thrive or vomiting | 18 | — |
| Ambiguous genitalia | 3† | — |
| Precocious puberty | — | 15 |
| Comatose | — | 1 |

*Two designated male at birth
†All with 3β-HSD deficiency

proportion of salt losers was increased in group 2 compared with group 1 ($p<0{\cdot}01$). In group 2 a lesser proportion of the patients were boys, although the difference in the male to female ratios between the two groups was not significant ($p>0{\cdot}1$).

Table 3 shows the presenting features of the patients studied.

Nineteen families yielded several cases, the diagnosis being the same for each. In eight cases knowledge of an older affected sibling led to earlier diagnosis. In the remaining cases (all girls) with an older sibling diagnosis was made in the neonatal period due to ambiguous genitalia, and we cannot say whether knowledge of adrenal hyperplasia in the older sibling had any effect on the diagnosis. One female non-salt loser born in 1949 was diagnosed at the age of 10 only after the diagnosis had been established in her younger sister aged 3.

## Discussion

The consequences of delayed diagnosis of congenital adrenal hyperplasia are well known,[17] and for these reasons neonatal screening has been advocated.[10 18] Others have suggested that the condition is easily diagnosed in the neonatal period and there is no need for neonatal screening.[14] As part of our assessment of the need for a screening programme in Birmingham we reviewed patients with congenital adrenal hyperplasia who had attended Birmingham Children's Hospital over 27 years. We chose to study the data with respect to the year of birth, and 1970 was important for several reasons: assays for 17-OHP became available then for the first time in this region, the number of paediatricians increased, and the appointment of a paediatric endocrinologist made the disease a major interest in the region.

For an autosomal recessively inherited disorder the expected male to female ratio is 1·1. In our study the overall ratio was 2:3, but when the year of birth was taken into account we found that, for children born in 1970 onwards, the ratio was closer to the expected 1:1. Furthermore, the prevalence of salt loss when related to the year of birth was significantly higher for children born in 1970 onwards. Although the numbers in our groups were small, these findings may suggest that there were fewer unidentified deaths among salt losing boys born after 1970. We are aware that during the period of this study two deaths occurred at Birmingham Children's Hospital for which findings at necropsy were consistent with adrenal hyperplasia. Both infants were boys, born in 1962, who died at 20 days and 4 weeks of age, respectively. The pattern of referral may, however, have changed over the period of study, and more selective referral to the Children's Hospital with fewer referrals of non-salt losing patients could have contributed to our findings.

Although in girls the condition is often diagnosed in the newborn period, in this study only half of the diagnoses in girls were made within 24 hours of birth; in some cases the diagnosis was not made until the child approached her teens. In addition, four genetic females were assigned male sex at birth. We are not aware of any incorrect assignments of sex after 1971, and all the girls in whom the diagnosis

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was made late were born before 1970. Among the girls born in 1970 onwards the condition was diagnosed in all but one by 2·5 months (and in 92% within two weeks of birth), suggesting earlier diagnosis in recent years. Interestingly, detection in boys increased from 1970 onwards (Table 1). An abnormality of the male genitalia at birth is not easily discernible and therefore cannot explain this; improved clinical awareness of electrolyte distburbances in male infants seems more likely

We cannot provide data on the incidence of congenital adrenal hyperplasia in the West Midlands as not all cases are referred to the Children's Hospital and some patients may have died with the condition undiagnosed. In addition, the immigrant population changed over the period of our study, and this may have had an effect on the incidence. Rudd, however, looked at data over one year from neonates born at eight major maternity units in the West Midlands.[19] There were 24 750 births, and congenital adrenal hyperplasia was diagnosed in four children (three girls and one boy), giving a prevalence of 1 in 6188. This is much higher than the figure quoted by Wallace *et al* in Scotland (1 in 13 401), obtained by neonatal screening,[8] and comparable with the figure calculated by Hubble for Birmingham in 1966 (1 in 7255) from case surveys. Although Rudd's data concerned only one year, they suggest that the rate of diagnosis by a non-screening procedure in this region is consistent with the expected incidence.

Our overall figures verify the finding of Lebovitz *et al* that congenital adrenal hyperplasia frequently remains undiagnosed in the neonatal period[10] but show that the diagnostic rate improved in the 1970s compared with that of previous years in the West Midlands. The reasons for this improvement are probably improved clinical awareness and better diagnostic tests. The major advantage of neonatal screening is the prevention of incorrect assignments of sex and death due to adrenal crisis, and we are not aware of the occurrence of either of these events since 1970. The value of earlier diagnosis in those infants who would be detected clinically, but later than by a screening programme, is not known, and it is therefore difficult to justify screening for this reason alone. Neonatal screening is not without problems; in particular, the interpretation of 17-OHP concentrations in premature or sick newborn infants is difficult. The anxiety generated by false positive results needs to be balanced against the potential advantages of a screening programme.

We are at present not convinced of the need for a neonatal screening programme for congenital adrenal hyperplasia in Birmingham or in the United Kingdom as a whole

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# Endotracheal resuscitation of preterm infants at birth

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SUMMARY The adequacy of initial ventilation in 21 preterm babies (25-36 weeks' gestation), who required endotracheal intubation and positive pressure ventilation, were studied. Pressure and flow were measured at the proximal end of the endotracheal intubation tube and expiratory volume calculated from the flow trace. The results were compared with those from a group of 26 term infants who also required resuscitation. Five of 21 preterm babies (24%) had adequate tidal ventilation with the first inflation. This rose to seven of 21 (33%) by the third inflation. This was significantly less than the results in the term infants ($\chi^2=4\cdot38$ $p<0\cdot05$). Respiratory reflex responses to resuscitation were seen in 41% of inflations in preterm and 56% of inflations in term infants. There was a significant correlation between reflex activity and adequate ventilation in the preterm group ($\chi^2=11\cdot83$, $p<0\cdot001$) but not in the term group ($\chi^2=0\cdot212$, p=NS). No correlation was seen between initial ventilation and outcome.

Endotracheal intubation with positive pressure ventilation is the definitive method of resuscitation of the newborn. Although endotracheal intubation resuscitation is empirically successful, relatively little work has been published on the mechanics of ventilation, and nearly all these studies have been concerned with term infants. This paper aimed to assess the adequacy of initial ventilation in preterm babies and to compare this with the group of term babies requiring resuscitation. Previous studies by Ditchburn *et al*,[1] Hey and Kelly,[2] and Hull[3] used a volume limited system rather than a pressure limited one and they were not able to measure tidal volumes directly.

## Subjects and methods

Over 1000 deliveries were attended. Babies were transferred after birth to our modified Vickers resuscitaire, details of which have been described previously.[4 5] Endotracheal intubation followed standard criteria—that is, apnoea with a heart rate less than 100 at two minutes, or apnoea and a heart rate less than 60 at any time At some deliveries an oesophageal pressure transducer was passed at intubation as the laryngoscope was withdrawn. Inflation pressure was about 30 cm water and was maintained for one second at a rate of 30/minute—that is, one second in, one second out. In a few cases the initial inflation was longer—three to five seconds. Resuscitation was continued until adequate respiration was established and the babies were subsequently managed on usual clinical criteria. The study was approved by the north Nottingham ethical committee.

**Equipment.** Babies were intubated with Coles's shouldered endotracheal tubes (size 12–14). A pneumotachograph (Fleish type 0) was attached to the endotracheal tube proximal to the T piece to measure flow with a linear response to above 15 l/minute. Inflation pressure was measured via a port close to the endotracheal intubation tube (SE Labs 4–86) Oxygen was supplied to the T piece through a spring loaded pressure limiting valve and the pressure delivered by occluding the T piece with a finger. In 33 cases (eight preterm, 24 full term) an oesophageal pressure transducer (Gaeltec) mounted on a 7FG catheter was used to validate the babies own respiratory efforts All signals were recorded on tape for later playback and the first three inflations subsequently displayed against time on an oscillograph for analysis.

**Analysis.** Time of inflation and plateau inflation pressure were measured from the pressure trace and tidal volume from the area under the flow curve using a 'Hipad' Digitiser (Houston Instruments) and commercial computer program.

## Results

Table 1 gives birth details of the babies studied. In the term group of 26 babies all were born by

Table 1 *Details of infants studied*

| | *Preterm (n=21)* | *Full term (n=26)* |
|---|---|---|
| Gestation: | | |
| Mean (SD) | 31·5 (2·7) | 39·5 (1·[illegible]) |
| Range | 25–36 | 37–42 |
| Birthweight | | |
| Mean (SD) | 1·5 (0·5) | 3·1 (0·[illegible]) |
| Range | 0·77–3·02 | 2·[illegible]–4·5 |
| Inspiratory pressure | | |
| (cm $H_2O$) Mean (SD) | 27·3 (4·8) | 26·5 (5·5) |

Table 2 *No of infants with tidal exchange of less than 4·4 ml/kg*

| | *Preterm* | *Full term* | $\chi^2$ | *Significance* |
|---|---|---|---|---|
| First inflation | 5 of 21 | 11 of 26 | 1·04 | NS |
| Second inflation | 6 of 21 | 16 of 26 | 3·85 | $p<0·05$ |
| Third inflation | 7 of 21 | 20 of 26 | 7·33 | $p<0·01$ |
| All three | 18 of 63 | 47 of 78 | 4·38 | $p<0·05$ |

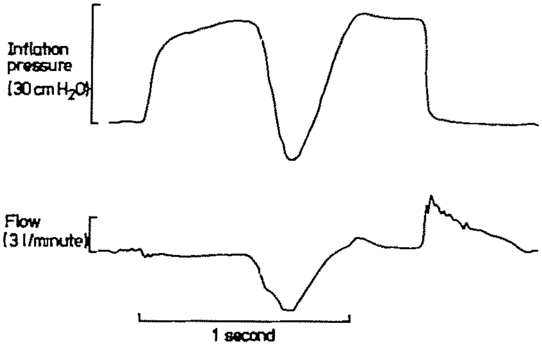
caesarean section, 11 performed after labour had started. Reasons for operative delivery were: fetal distress (n=5); failure to progress in labour (n=5); abruptio placentae (n=1), breech presentation (n=3) transverse lie (n=2), and one each with postmaturity, twins, maternal diabetes, small for dates, and cephalopelvic disproportion. In the preterm group of 21 babies 15 were delivered by caesarean section, 11 after labour had started The four elective deliveries were due to maternal hypertension or pre-eclampsia in three cases, and previous caesarean section plus hypertension in the fourth. Of the six vaginal deliveries, there were three breech deliveries, two low forceps, and one normal delivery.

The first three inflations were analysed. Inflation pressures were comparable in the two groups and a prolonged first inflation was given in three preterm infants. Adequate tidal exchange, defined as >4·4 ml/kg was obtained in less than a third of the preterm infants in the first three breaths (Table 2) Table 2 shows that inflations in term infants were more successful The $\chi^2$ tests on the first three inflations show that from the second inflation there was a significant difference between the two groups, with more term infants achieving adequate ventilation

Three patterns of neonatal respiratory reflexes were seen Head's paradoxical reflex was identified by the fall in the inflation pressure from the plateau accompanied by inspiratory flow; a rejection response was identified by an increase in the plateau pressure with or without expiratory flow; both responses were seen during a single inflation (Figs 1–3). In 19 cases an oesophageal pressure trace was

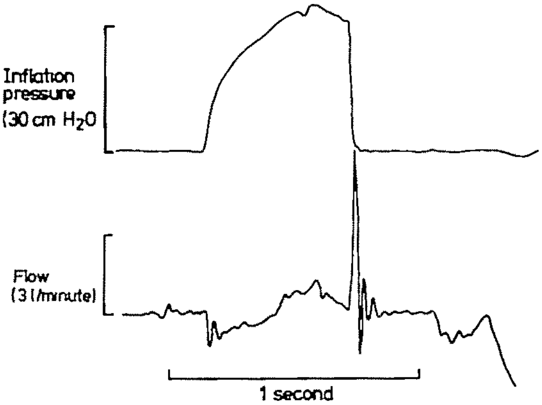
1.

Inspiration response



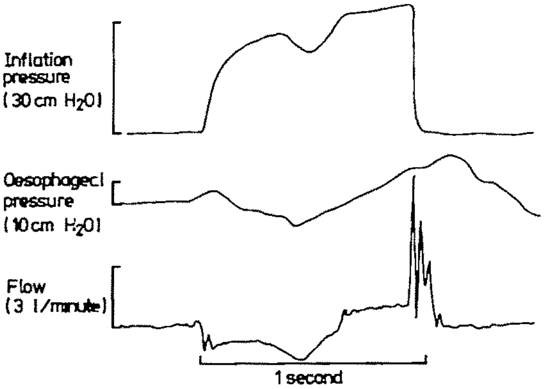
2.

Rejection response



3.

Combined inspiration-rejection response



Figs 1–3 *Examples of inspiratory, rejection, and combined response from preterm group of babies Inspiratory flow is in downward direction Oesophageal trace in fig 3 confirms initial active inspiration (downward movement) with inspiratory flow and dip in inflation pressure trace followed by active expiration (upward movement) associated with expiratory flow against inflation pressure*

obtained and confirmed our designations in all cases. A reflex was seen in 26 inflations in the preterm group (41%) Fifteen were a Head's paradoxical reflex, five a rejection response, and six both reflexes in a single inflation. There was a correlation between tidal exchange and presence of a reflex response (Table 3) There was no obvious difference between the different reflexes and the associated tidal exchange, but the numbers are too small for valid statistical analysis. Of particular importance—of 37 inflations with no reflex activity, only four achieved adequate tidal exchange, and three of these had been preceded by reflex activity in a previous breath.

Any type of reflex was seen in 44 inflations in the term infants (56%), and this comprised 16 Head's reflexes, 25 rejection responses, and three combined responses In contrast to the premature infants, there was no significant correlation between presence of reflex and adequate tidal exchange (Table 4), although if a reflex was present the tidal exchange was more likely to be in the upper part of the inadequate range—that is, one to two dead space volumes

Within the group of preterm infants there was no relation between gestational age and either tidal exchange or presence of reflex response. The numbers, however, were small after subdividing into gestational age groups, and only three babies were less than 30 weeks' gestation.

**Outcome.** There were four deaths in the group of premature infants. All deaths were related to severe respiratory distress syndrome and occurred in the first 48 hours. Gestational ages of these four were; 25 weeks (two babies both second twins) and 31 weeks (two babies) Three of these had inadequate tidal ventilation in the first three breaths. The fourth, 25 weeks' gestation, initially had a 10–16 ml/kg tidal exchange but required positive pressure ventilation from birth to maintain adequate blood gases Overall, five of the babies required ventilation for respiratory distress syndrome and three required oxygen for more than 24 hours; there was no association between development of respiratory distress syndrome and initial tidal exchange in the first three breaths.

Table 3 *Premature resuscitation*

| *Tidal exchange (ml/kg)* | *Reflex present* | *No reflex* | *Total No* |
|---|---|---|---|
| <4 4 | 12 | 33 | 45 |
| >4 4 | 14 | 4 | 18 |
| | 26 | 37 | 63 |
| $\chi^2$=11 83 | p<0 001 | | |

Table 4 *Full term resuscitation*

| *Tidal exchange (ml/kg)* | *Reflex present* | *No reflex* | *Total No* |
|---|---|---|---|
| <4 4 | 16 | 15 | 31 |
| >4 4 | 28 | 19 | 47 |
| | 44 | 34 | 78 |
| $\chi^2$=0 212 | | Not significant | |

Although three of the four babies who subsequently died had reflex activity, the response to inflation was a poor indicator of outcome. Two of the 11 with reflex responses developed respiratory distress syndrome that required ventilation compared with three of the 10 who showed no response.

Exposing the preterm baby to labour might be expected to influence the response to resuscitation, but no such effect was seen in this relatively small study. Three of the seven babies delivered electively had no response compared with seven of 14 delivered vaginally or by emergency caesarian section.

## Discussion

One of the difficulties in this study was the lack of data on inspiratory volumes. In a large number of the preterm babies there was a leak of gas around the endotracheal tube when the positive pressure was applied. This leak made analysis of inspiratory volumes impossible. A clinically important volume of gas might have entered the babies' lungs but was retained there to form a functional residual capacity. We feel that this is unlikely to have been a large source of error as there were 11 babies in the preterm group, in whom there was no leak around the endotracheal intubation tube. Eight had no functional residual capacity formed in the first three breaths, and in the other three increments in functional residual capacity that were not considered to be due to leak were all associated with adequate expiratory volumes. In the term group where leak around the tube was less of a problem, a functional residual capacity was formed in 10 of 23 babies by the third breath. It is also, of course, possible that a functional residual capacity was formed in the time from delivery to insertion of the endotracheal tube.

The use of 4·4 ml/kg to define adequate tidal exchange is based on estimations of anatomical dead space of 2·2 ml/kg.[6] This figure is independent of age Two dead spaces is 4·4 ml/kg, and by definition half of the gas will be taking part in gaseous exchange. Our decision to use two dead spaces as a cut off seems appropriate but is essentially arbitrary.

It seems that endotracheal intubation resuscitation of preterm infants depends, to a great extent, on reflex responses, particularly the Head's reflex, although whether strictly speaking it corresponds to the original reflex described by Head is unclear.[7] These inspiratory gasps were related to the inflation but there was no temporal relation to the start of the inflation as seen in the description of the augmented inspiratory reflex by Greenough *et al.*[8] Likewise, there was no evidence that a higher inflation pressure was more likely to stimulate a gasp. Cord pH and fetal scalp pH samples were not recorded in this study and so we are unable to correlate reflex response with degree of asphyxia. If work on animals[9] is applicable to human preterm resuscitation one might expect the degree of asphyxia to be a major determinant of these reflexes. It is important to know whether babies who exhibited reflex responses are those who are only mildly asphyxiated. If so, the strategies to maximise reflex responses are of less clinical importance than those that effect adequate passive ventilation.

Delivery after labour has started might influence effectiveness of resuscitation. It may be associated with asphyxia, particularly in the preterm group, but there may also be benefits to the fetus such as stimulating absorption of lung fluid and surfactant release. The benefits are more likely to be apparent at a later stage, however, and mechanical factors are probably more important than biochemical factors in response to initial resuscitation. In our data there was no evidence of an effect of labour on reflexes or tidal exchange for either the term or preterm groups, but it is difficult to draw any conclusions from this as emergency and elective section babies are obviously selected groups.

The underlying assumption of this study is that early establishment of adequate ventilation is important in preterm infants and that if this can be achieved in the first few inflations then outcome will be improved. We have been unable to show any correlation between initial resuscitation and outcome but the numbers are small, and many other factors including gestational age and degree of asphyxia at birth also affect subsequent progress.

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# Plasma atrial natriuretic peptide and spontaneous diuresis in sick neonates

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SUMMARY Plasma concentrations of immunoreactive human atrial natriuretic peptide (human ANP) were sequentially determined in 12 infants with respiratory distress syndrome (RDS) or meconium aspiration syndrome (MAS) during various phases of diuresis to elucidate the role of human ANP in the occurrence of spontaneous diuresis in the newborn. Plasma immunoreactive ANP concentrations during the diuretic as well as the maximum diuretic phase were significantly ($p<0.001$) higher than during the prediuretic phase. A gradual decrease occurred during the post diuretic phase, returning to prediuretic values after one week of life. Significant natriuresis, increased glomerular filtration rate, mild hyponatremia, and decreased blood pressure were observed in the diuretic phase in all the cases studied. These results suggest that hypersecretion of human ANP may play an important part in initiating spontaneous diuresis in sick neonates.

Spontaneous diuresis is often delayed in ill neonates, particularly in those who have suffered birth asphyxia and those with respiratory distress syndrome (RDS).[1] Failure to initiate spontaneous diuresis is related to the degree of severity of RDS or meconium aspiration syndrome (MAS) [2] Despite extensive studies on postnatal renal adaptation, the physiological importance of the renal function responsible for this diuresis has not yet been fully understood.[3] Recently, atrial natriuretic peptide (ANP), with potent natriuretic and diuretic activities, has been isolated from rat and human atrial tissues.[4] It has been reported that an intravenous infusion of synthetic human ANP causes a dramatic increase in sodium excretion and urinary volume in animals as well as in man.[5] The physiological role of endogenous human ANP in the newborn, however, remains unknown. The purpose of this study was to clarify the role of human ANP in the incidence of spontaneous diuresis in relation to the renal function in neonates with RDS or MAS

## Patients and methods

Twelve neonates (nine boys and three girls), who were transferred to the neonatal intensive care unit, Kansai Medical University Hospital, for treatment of RDS (n=5) or MAS (n=7), were studied during the first four days of life. Age at admission was 3·2 (SD 4·4) hours. Informed consent was obtained from each patient's parents. The mean gestational age and birth weight of the infants was 35·5 weeks (26–41 weeks) and 2208 g (1040–4030 g), respectively. Nine infants were ventilated with a Bourns BP 2001 respirator The mean volume of fluid administered (ml/kg/day) was 61 8 (14·2) on day 1, 68·3 (17·6) on day 2, 84·5 (17·4) on day 3, and 104·3 (19·4) on day 4, respectively The fluids consisted of 10% glucose supplemented with calcium (100 mg/kg/day) until the third day of life, after which sodium chloride (35 mmol/l) and potassium chloride (20 mmol/l) were added. All fluid intake was administered parenterally. The mean fluid intake over each eight hour period was calculated from a fluid balance chart monitered every hour. Urine was collected in a collecting bag for all male infants and one female infant so as to measure directly the volume. In two other female infants the urine volume was calculated by weighing nappies immediately after voiding Urine was consecutively collected during the first four days of life: onset of diuresis was defined as urine output greater than 1 ml/kg/hour, and the maximum urine output as the greatest output during the first four days of life by checking the urine volume every hour The diuretic phases were arbitrarily divided into four eight-hour periods: the first (prediuretic) phase was defined as the beginning of urine collection just after admission at 3·0 (4·7) hours of age; the second (diuretic) phase as the onset of diuresis with urine volume greater than 1 ml/kg/hour occurring at 17·5 (11·2) hours of age; the third (maximum diuretic) phase as the maximal urine output following the diuretic phase at a mean age of 43·3 (18·3) hours; the fourth (post diuretic) phase as 24 hours after maximum diuretic phase at a mean age of 67·3 (18·3) hours The arterial pressure was measured every 30 minutes in the right arm using the Doppler ultrasound technique throughout the study.

Blood samples were obtained at the mid point of urine collections to determine human ANP, creatinine, urea, nitrogen, glucose concentrations, and electrolytes. Urine collected from all male infants and one female infant were pooled for the determination of osmolality, urinary sodium, potassium, and creatinine concentrations to calculate fractional excretion of sodium (FENa) and urine:plasma osmolar ratio in each phase. Creatinine clearance (Ccr) FENa, osmolar clearance (Cosm), and free water clearance ($CH_2O$) were determined using standard formulas shown below:

$$\text{FENa}\ (\%) = \frac{\text{UNa}\times\text{SNa}}{\text{Ucr}\times\text{Scr}}\times 100 \quad \text{Ccr}\ (\text{ml/minute}) = \frac{\text{Ucr}\times\text{V}}{\text{Scr}}$$

$$\text{Cosm}\ (\text{ml/minute}) = \frac{\text{Uosm}\times\text{V}}{\text{Posm}},\ \text{CH}_2\text{O}\ (\text{ml/minute}) = \text{V} - \text{Cosm}$$

Where V indicates urine flow (ml/minute); SNa, serum sodium concentration (mEq/l); UNa, urinary sodium concentration (mEq/l); Scr, serum creatinine (mg/dl) Ucr, urinary creatinine (mg/dl), Posm, plasma osmolality (mOsm/l); and Uosm, urinary osmolality (mOsm/l).

To determine the sodium balance for each phase sodium intake was calculated from the sodium content of fluids, medicine, and blood products administered. Sodium output was measured in a pooled urine sample for each phase

Determinations of creatinine, urea, nitrogen, and glucose concentrations, and electrolytes in serum and urine were performed using an autoanalyser (Beckman Astra-8), and urine osmolality was measured by freezing point depression (Fiske OR osmometer).

**Radioimmunoassay of human ANP.** Plasma (0·5 ml) was extracted by ODS cartridges (Sep-Pak, Waters Associates, Milford, Minnesota), as reported.[6] Radioimmunoassay of human ANP was performed by using an antibody generated in rabbits immunised with human α-ANP$^{1-28}$ (Peptide Institute, Osaka, Japan) coupled to bovine thyroglobulin by carbodi-imide. The antibody cross reacted fully with α-human ANP$^{1-28}$, rat (r) ANP$^{1-28}$ (40%) but less with α-human ANP$^{7-28}$ (2–5%), rANP$^{5-28}$ (atriopeptin III), rANP$^{5-27}$ (atriopeptin II), and rANP$^{5-25}$ (atriopeptin I), and not at all with angiotensin II, arginine vasopressin, nor bradykinin The assay buffer was 50 mM phosphate buffered saline (pH 7·4), containing 0·1% bovine serum albumin, 1 mM edetic acid, 0·1% triton X-100, and 500 U/ml aprotinin. The incubation mixture, which consisted of 0·1 ml standard human α-ANP or plasma extract and 0·1 ml antibody (final dilution—1/10 000), was preincubated at 4°C for 24 hours, followed by the addition of 0·1 ml $^{125}$I-labelled α-human ANP (Amersham International, Tokyo, Japan). After additional incubation at 4°C for 24 hours, bound ligands were separated from free ligands by the double antibody method. The lowest concentration of human ANP yielding a binding significantly different from that found in the absence of standard α-human ANP at the 95% confidence interval was 3 pg/tube, and the 50% intercept was 20 pg/tube. The minimum detectable concentration of immunoreactive human ANP in plasma was 30 pg/ml. The interassay and intraassay coefficients of variations were less than 10%. The recovery of immunoreactive human ANP applied to Sep-Pak cartridge was 50–60%. All values were corrected for the recovery during the extraction procedure.

Statistical analysis was performed by Student's $t$ test or Welch's $t$ test following the F-test. Data were presented as mean (±SD)

## Results

The Figure shows that the mean plasma concentration of immunoreactive human ANP was significantly (p<0·001) higher during the diuretic phase (305·4

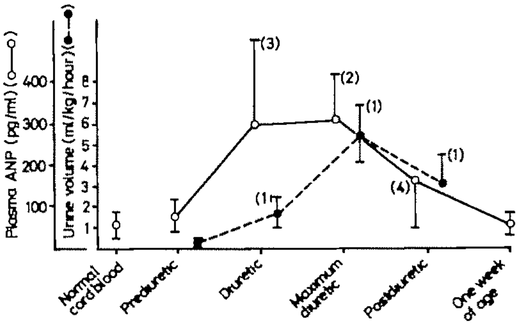

Figure *Sequential changes of plasma human ANP concentrations and urine volume in newborn infants with RDS or MAS. Open circles indicate mean plasma concentrations of immunoreactive human ANP and closed circles indicate mean urinary volume during various diuretic phases, bars show standard deviation*

(208·7) pg/ml) and the maximum diuretic phase (314·0 (107·2) pg/ml), than during the prediuretic phase (80·6) (40 2) pg/ml), and that it gradually decreased during the post diuretic phase (168·4 (120·9) pg/ml), returning to prediuretic concentrations after one week of age (62·7 (27 4) pg/ml). Plasma concentrations of immunoreactive human ANP during the prediuretic phase and after one week of age were comparable with those of normal cord blood (61·3 (22·5) pg/ml; n=7) and those of healthy adults (40 (20) pg/ml); n=20). There were significant (p<0·01) inverse correlations between immunoreactive human ANP concentrations and plasma osmolality (r=−0·62), or mean arterial blood pressure (r=−0·58), in the prediuretic and diuretic phases, while plasma human ANP concentrations did not correlate with body weight nor serum sodium concentrations.

Tables 1 and 2 show the studies of renal function during each phase. The increased urine output during the diuretic phase was associated with a significant increase of FENa (p<0·01). There were also significant increases in creatinine clearance (p<0·05) and free water clearance (p<0·01) during the maximum diuretic phase. The serum sodium concentrations decreased slightly during the diuretic phase. Output:intake ratio was significantly decreased during the prediuretic phase (p<0·01). Systolic and diastolic blood pressure were slightly decreased during the diuretic phase, but returned to the basal values during the maximum diuretic and post diuretic phases Pulse rate was unchanged throughout the study.

## Discussion

This study clearly shows that an increase of plasma immunoreactive human ANP concentrations coincided with the occurrence of spontaneous diuresis in neonates with RDS or MAS. Plasma immuno-

Table 1 *Mean (SD) changes in body weight, plasma atrial natriuretic peptide (ANP), serum sodium, blood pressure, and pulse rate during various phases of diuresis in newborn infants with RDS or MAS*

| *Variable* | *Phase* | | | |
|---|---|---|---|---|
| | *Prediuretic* | *Diuretic* | *Maximum diuretic* | *Post diuretic* |
| Age (hours) | 3 0 (4 7) | 17 5 (11 2) | 43 3 (18 3) | 67 3 (18 3) |
| Bodyweight (gm) | 2145 (930) | 2223 (901) | 2143 (887) | 2089 (883) |
| Plasma human ANP (pg/ml) | 80 6 (40 2) | 305 4 (208 7)* | 314 0 (107 2)† | 168 4 (120 9) |
| Serum sodium (mmol/l) | 139 (3) | 136 (4) | 137 (3) | 138 (3) |
| Arterial pressure (mm Hg) | | | | |
| Systolic | 59 (6) | 55 (4) | 60 (6) | 64 (7)‡ |
| Mean | 47 (5) | 45 (4) | 49 (6) | 53 (7) |
| Diastolic | 36 (4) | 34 (2) | 38 (5)¶ | 40 (5)‡ |
| Pulse rate (beat/minute) | 153 (17) | 149 (18) | 143 (10) | 139 (6) |

†p<0 001, *p<0 01 *v* prediuretic phase, respectively
‡p<0 01, ¶p<0 05 *v* diuretic phase, respectively

Table 2 *Mean (SD) changes in renal function tests and fluid and sodium balance during various phases of diuresis in newborn infants with RDS or MAS*

| *Variable* | *Phase* | | | |
|---|---|---|---|---|
| | *Prediuretic* | *Diuretic* | *Maximum diuretic* | *Post diuretic* |
| Creatinine clearance (ml/minute) | 0 97 (0 64) | 1 68 (1 40) | 2 29 (1 5)‡ | 2 40 (1 70)‡ |
| Fractional excretion of sodium (%) | 0 45 (0 45) | 7 1 (6 8)* | 5 6 (4 5)* | 4 3 (4 7)‡ |
| Osmolality (mOsm/kg) | | | | |
| Plasma | 288 (6) | 287 (6) | 288 (10) | 289 (7) |
| Urine | 520 (285) | 225 (87)* | 187 (92)* | 248 (125)* |
| Free water clearance (ml/minute) | −7 4 (1 4) | 2 2 (3 9)† | 143 (119)*¶ | 7 3 (5 1)* |
| Fluid balance (ml/kg/hour) | | | | |
| Intake | 2 6 (1 0) | 2 6 (0 9) | 3 6 (1 3)§ | 4 1 (1 2)* |
| Output | 0 3 (0 2) | 1 8 (0 7)† | 5 6 (1 3)*¶ | 3 2 (1 4)† |
| Output/intake (%) | 13 (8) | 81 (43)† | 172 (67)†¶ | 94 (38)† |
| Sodium balance (mmol/kg/hour) ($\times 10^4$) | | | | |
| Intake | 0 | 70 (140) | 800 (800) | 1200 (1200) |
| Output | 70 (80) | 1400 (1100)* | 2660 (1440)† | 3250 (1700)† |

†p<0 001, *p<0 01, ‡p<0 05 *v* prediuretic phase, respectively
¶p<0 01, §p<0·05 *v* diuretic phase, respectively

reactive human ANP concentrations increased during the diuretic and maximum diuretic phases, followed by a gradual decrease during the post diuretic phase, and returned to prediuretic values after one week of age. These changes were observed not only in mature infants, but also in premature infants. Plasma immunoreactive human ANP concentrations were almost the same in mature and premature sick neonates. These results suggest that human ANP is normally secreted in neonates, irrespective of maturity.

The major renal effect of human ANP in adults is an increase in glomerular filtration rate which does not affect renal blood flow but shifts the glomerular balance toward natriuresis.[7] In fact, a noticeable natriuresis and an increase in glomerular filtration rate were observed during spontaneous diuresis in all cases studied. It has recently been reported that secretion of endogenous human ANP stimulated by the extracellular volume expansion is responsible for the observed natriuresis and diuresis.[8–10] The mechanism by which human ANP is secreted in the newborn has not yet been established. As fluid restriction is normally used to treat patients with respiratory problems volume expansion has been considered to be less common in the newborn period. Costarino *et al*, however, showed that the diuresis in patients with RDS is a water diuresis resulting from an endogenous water overload, and that spontaneous diuresis after birth represents the infant's physiological response to extracellular water load.[3] In this study positive water balance was observed in the prediuretic phase, and negative correlation between plasma human ANP concentrations and plasma osmolality was also observed. Therefore, extracellular volume expansion induced by the relative overhydration and the endogenous water overload may lead to the release of human ANP in the newborn period. Furthermore, it has been shown that plasma renin activity and angiotensin II concentrations are increased during the newborn period,[11] causing an increased extracellular volume in the neonatal period. Taken together, it seems possible to speculate that the extracellular volume expansion in the early neonatal period may trigger release of human ANP through the distension of atrial wall or the increase of intra-atrial pressure or both. We speculate that endogenous human ANP, possibly stimulated by an extracellular volume overload, is one humoral factor responsible for the spontaneous diuresis in sick neonates.

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# Correlation of specific gravity and osmolality of urine in neonates and adults

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SUMMARY There is good correlation between the specific gravity and osmolality of urine obtained from neonates and adults, if specimens contain neither protein nor glucose. The regression equations between specific gravity and osmolality, however, differ considerably between the two age groups, maturation to the adult regression occurring within the first 5 years of life. Specifically derived regression equations should therefore be used when predicting urine osmolality from measurement of specific gravity in neonates.

The osmolality of urine is the definitive measure of its concentration. Under normal physiological conditions low urine osmolality equates with hydration, and high urine osmolality with dehydration The ability of neonates to concentrate urine is lower than that of adults, but the capacity to dilute urine is similar. In a non-uraemic, normonatraemic, and normoglycaemic neonate, therefore, urine osmolality maintained between 75 mosmol/kg–300 mosmol/kg indicates adequate hydration, values outside these ranges suggest overhydration and dehydration, respectively [1]

The necessity for monitoring urine osmolality in neonates to estimate fluid balance may make heavy demands on the laboratory Osmometers are expensive and unsuitable for use in the wards without the help of a technician. The specific gravity of urine, traditionally measured in the ward, also reflects concentration, but the prediction of urine osmolality from specific gravity measurement may be unreliable in unskilled hands.[2] In addition, abnormal concentrations of glucose and protein in the urine cause appreciable increases in specific gravity without affecting osmolality. Finally, measurement by traditional flotation hydrometry requires a large volume of urine. All these factors militate against the use of specific gravity as a measure of urine concentration in neonates

Despite recent interest in the measurement of specific gravity as an indicator of urine concentration in children, the influence of age on the relation between specific gravity and osmolality has not been defined [3] We studied the association between urine specific gravity measured by refractometry, and osmolality, to assess the practicability of measuring the urine concentration of neonates accurately in the ward; we also assessed the influence of age on the relation between specific gravity and osmolality.

## Material and methods

We collected 100 urine samples from 21 neonates in the special care baby unit, the babies had been born at 28 to 32 weeks' gestation and mean (SD) weight was 2100 (940) g. Single specimens of urine were collected from 22 healthy babies born at full term, 88 children from a paediatric ward (age range 1–70 months), and from 59 healthy adults The specimens were not taken at a particular time, nor were they preserved. Urine was tested for the presence of glucose and protein using the Ames Uristix, and those specimens showing positive results were excluded.

Osmolality was measured on fresh urine samples by freezing point depression osmometry (Advanced Instruments Model 3D), and specific gravity by a hand held refractometer (Atago, Uricon), which was corrected for temperature before use

Data were analysed by the method of least squares and by the linear regression method of Deming.[4] Statistical comparison was by Student's *t* test

## Results

Fig. 1 shows the 95% confidence limits of the Deming regression of osmolality to specific gravity for neonates and for adults.

The Deming regression equations were. (i) neonates (n=96)—osmolality = 20004 (specific gravity)−20025, r=0·933, SE Deming regression in Y direction = 23·9; and (ii) adults (n=59)—osmolality = 33194 (specific gravity)−33247, r=0·990, SE Deming regression in Y direction = 45·6. The Standard Errors of the slopes were 795 and 620, respectively, and the slopes were significantly different ($p<0·0001$).

Fig. 1 shows the results from the samples of urine taken from the neonates born at term, and from the infants aged between 1 and 70 months Those from the neonates fell within the limits previously defined for the neonates on the special care baby unit, but the infants' data show a progression in the results from the neonatal to the adult association.

To study this progression we ranked the data on specific gravity and osmolality from all infants in 10 month age bands. Using equation 2, the osmolality of each urine sample was calculated from the measurement of specific gravity. The measured osmolality was expressed as a percentage of the calculated value (Δ) after correction of values to account for the common intercept of both regression equations which is not at zero, but at an osmolality of 27·5 mosmol/kg.

$$\Delta = \frac{(\text{measured osmolality} - 27\cdot5)}{(\text{calculated osmolality} - 27\cdot5)} \times 100$$

Fig. 2 shows the association between the mean Δ (SE) of each age band and the mean age of each band. There is rapid progression towards the adult association of specific gravity and osmolality during the first two years of life which is completed around the fifth year.

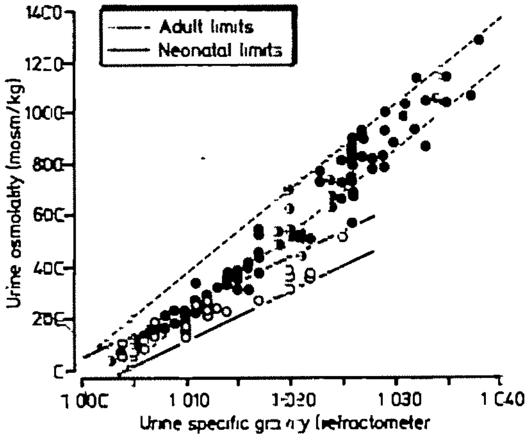

Fig. 1 *Association of specific gravity and osmolality of urine in full term healthy neonates (●) and children aged between 1 and 70 months (○) 95% confidence limits derived from data from neonates in special care baby unit, and healthy adults.*

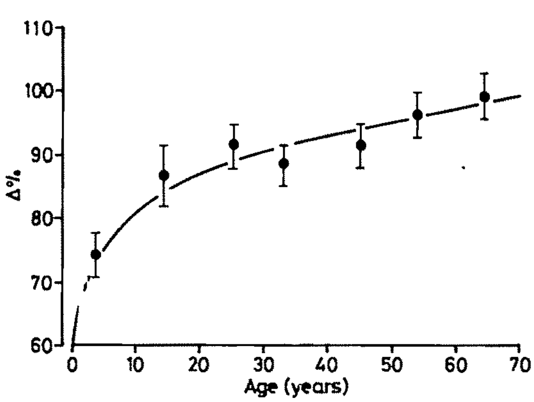

Fig 2 *Change in association of specific gravity and osmolality of urine from neonatal to adult pattern with age*

## Discussion

There is good correlation between urine specific gravity, measured by refractometry, and osmolality in neonates, but the association is different from that found in adults The change is probably a reflection of the reduced reabsorption of small molecules and low molecular weight proteins by the renal tubules that occur during early infancy and childhood. In particular, the reduced percentage reabsorption of amino acids,[5] and low molecular weight proteins such as microglobulin,[6] results in a relatively large increase of specific gravity when compared with osmolality. As proximal tubular function matures, so the association of urine specific gravity and osmolality approaches the adult pattern, which approximates to that produced by the predominant molar constituents of urine—sodium, potassium, and urea. Although the mean age of the infants in the special care baby unit ranged from 28 weeks to term (a period of tubular maturation), the scatter of the values for osmolality and specific gravity of urine suggests that changes in the composition of the urine which were important enough to affect the association between them, do not occur during this period.

As an easy measurement of the specific gravity of urine in the ward refractometry is accurate enough to predict the osmolality of urine in neonates if samples containing protein and glucose are excluded. A specifically derived neonatal regression, however, should be used.

We thank the departments of paediatrics and medical illustration for their help

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## Twenty five years ago

### The measurement and meaning of pyuria

*J M Stansfield (Durham)—Arch Dis Child* 1962;**37**:257–62

Twenty five years ago the usual method of estimating the degree of pyuria was to place a drop of urine under a microscope and to count the number of cells within a high power field (HPF). While this technique could reveal gross degrees of pyuria, there may be only a few pus cells in some cases of pyelonephritis In this paper the author pointed to the incongruity of accurately counting cells in blood and cerebrospinal fluid while accepting crude estimations of the cell numbers in urine. He advocated the measurement of pyuria using a counting chamber (Neubauer). In uncentrifuged urine one cell per HPF was found to be equivalent to 250–500 cells per $mm^3$. Cell counts per HPF had higher coefficients of variation than those in which a counting chamber was used. Urine cell counts were made on 2000 consecutive admissions to a general paediatric unit; nearly 5% of the boys and 27% of the girls were found to have more than 10 white cells per $mm^3$. These findings reflected the frequency with which naturally voided urines could be contaminated The importance of pyuria could only be judged from cell counts on clean midstream or catheter specimens. The author considered that a finding of 10 or more cells per $mm^3$ was pathological By combining cell and bacteriological counts he classified pyuria into three categories. (a) *Contamination*· whatever the cell count in an ordinary specimen a clean specimen will contain less than 10 cells per $mm^3$ and the culture will be sterile or the bacterial count less than 10 000 per ml, (b) *Urinary tract infection*: a clean specimen contains 10 or more cells per $mm^3$, often in clumps or casts, and the bacterial count will be over 100 000 per ml; and (c) *Unknown*: cells but not organisms are occasionally present in abnormal numbers in clean specimens. The author also recognised that pyuria may sometimes be absent in the presence of urinary tract infection, especially if it has been of long duration, but he considered that occasional difficulties of interpretation did not outweigh the value of the measurements

**Comment.** The value of white cell counts in urine is now generally recognised, although demonstraton of an appreciable bacteriuria by culture is essential for a definitive diagnosis In the acutely ill child the finding on microscopy of a raised urine cell count and visible bacteria may justify immediate treatment while awaiting the results of urine culture. Most laboratories now prefer the Fuchs-Rosenthal counting chamber to the Neubauer. It is, however, to be regretted that so few young doctors of today are encouraged to become self proficient in the simple techniques that used to be employed in ward side rooms

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# Comparison of intranasal and oral desmopressin for nocturnal enuresis

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SUMMARY A single blind dose response study of the effects of treatment with tablets containing 50–400 μg of desmopressin was conducted in 15 children with primary nocturnal enuresis. A dose response effect was seen, with the 100, 200, and 400 μg doses resulting in significantly more dry nights than when a placebo was used. The response after 200 μg was significantly different from that after 100 μg ($p<0\cdot02$) but not from that after 400 μg.

A randomised, double blind, double dummy, cross over study was then carried out in 30 children to compare the effects of a 20 μg dose given through a nasal pipette, a 200 μg tablet, and a placebo. The numbers of dry nights were significantly greater during both periods of treatment with desmopressin when compared with that using placebo, but there were no differences between the methods of taking the drug. After oral and nasal treatment 41% and 52%, respectively, of the patients improved by more than 50%. Nine children (31%) remained completely dry after treatment.

Desmopressin is a potent, long acting antidiuretic polypeptide that has been shown to be an effective treatment of enuresis both in children and adults when given intranasally.[1-4] An oral preparation of the drug has recently been developed, which is effective in the treatment of neurogenic diabetes insipidus.[5-7] The intranasal and the oral routes for giving desmopressin were compared in 10 children with diabetes insipidus and found to give equivalent results.[8] Encouraged by these findings, we sought to establish whether a tablet of desmopressin could be used to treat nocturnal enuresis. This study reports the results of a dose response trial of desmopressin given orally to 15 enuretics, followed by a double blind, double dummy, cross over, trial comparing oral, intranasal, and placebo preparations.

## Patients and methods

**Dose response study.** Nine boys and six girls, aged from 6 to 14 (mean 8·7, SD 2·9 years) with primary nocturnal enuresis were treated with oral desmopressin in a single blind dose-ranging study that was preceded and followed by a week without any treatment. After one week of taking placebo tablets the children were given tablets containing 50, 100, 200, and 400 μg desmopressin, in this sequence, for a week each. The number of dry nights each week was recorded, and the children were weighed every morning. Urine osmolality was estimated once a week from a urine sample taken at 5 am, and serum sodium concentrations were measured before and after treatment.

**Comparative study.** The second study comprised 20 boys and 10 girls, aged from 6 to 15 (mean 9·8, SD 2·5 years) with primary nocturnal enuresis. Each child had at least three wet nights a week during the period of observation. Half the children gave a family history of bed wetting, and 69% had tried one or more of the following treatments: enuresis alarm (n=18), intranasal desmopressin (n=7), tricyclic antidepressants (n=8), or anticholinergic drugs (n=6). All treatments were stopped at least four weeks before the period of observation. Patients with urinary tract infections, faecal soiling, or neurological or urological abnormalities, were excluded.

The study was designed as a randomised, double blind, double dummy, cross over trial of 200 μg desmopressin given orally, 20 μg desmopressin given intranasally, and placebo treatment. The periods of treatment were preceded and followed by one week of observation. For six weeks patients were allocated each of the following regimens at fortnightly intervals: placebo tablet and placebo nasal pipette for the first two weeks, followed by two weeks each on either intranasal or oral desmopressin, according to the double dummy, cross over design All drugs were taken at bed time, and there was no 'washout' period between the regimens as the cumulative effects have been shown to be small.[2 3] Patients or parents recorded on a diary card the number of wet nights during each period. In addition, bed wetting was recorded using an enuresis score (0=dry, 1=slightly wet, 2=very wet). Children were weighed each morning, and urine osmolality and serum sodium concentrations were determined at weekly intervals from a sample of urine taken at 5 am. Blood pressure and concentrations of albumin and creatinine in serum were measured regularly. Informed consent was obtained from all patients or parents, and the protocol was approved by the ethical committee of Malmo-Lund University.

**Statistical methods.** The results were expressed as mean (SEM). All data were tested for normality with the Wilk-Shapiro test. The paired Student's *t* test was used to analyse normally distributed data, and non-parametric tests (paired Wilcoxon signed rank test and $\chi^2$ test) were used for the others

## Results

**Dose response study.** The number of dry nights each week rose with each increasing dose of desmopressin (Fig. 1) Significant differences between the placebo treatments were seen at doses of 100 µg ($p<0{\cdot}05$), 200 µg ($p<0{\cdot}05$), and 400 µg ($p<0{\cdot}01$). The 200 µg dose produced a significant increase in the number of dry nights compared with the 100 µg dose ($p<0{\cdot}02$), but no difference was seen when the 200 µg and 400 µg doses were compared. Urine osmolality in specimens taken at 5 am increased weekly with the 400 µg dose, 1000 (45) mOsm/kg being significantly different from the measurement recorded when the placebo was being taken, of 851 (47) mOsm/kg, ($p<0{\cdot}05$). No side effects were recorded. No significant changes in bodyweight were seen except when the 400 µg dose was being taken; a significant increase over the preceding week occurred ($p<0{\cdot}01$). No significant differences between sodium concentrations in serum before and after treatment were found We concluded that a dose of 200 µg desmopressin taken orally was suitable for further controlled studies

**Comparative study.** Thirty patients entered the double blind study to compare the effects of desmopressin given either orally or intranasally. One boy withdrew after the study had started. During the observation period the mean number of dry nights a week was 2·2 (0·2), and this did not rise significantly when the placebo was being taken During both periods of treatment with desmopressin, the mean number of dry nights doubled (Fig. 2) when compared with placebo ($p<0{\cdot}001$), but there was no difference between the methods of giving the drug Several patients relapsed when the treatment had finished, but nine children (31%) remained completely dry.

In an attempt to grade the response to desmopressin the percentage improvement with both methods was compared with the level before treatment (Fig. 3) Nine patients taking tablets improved by 75–100%, and two of them were totally dry, while five and one patient, respectively, responded similarly to the drug given nasally. Seven patients did not respond to tablets, and only two did not respond to nasal treatment.

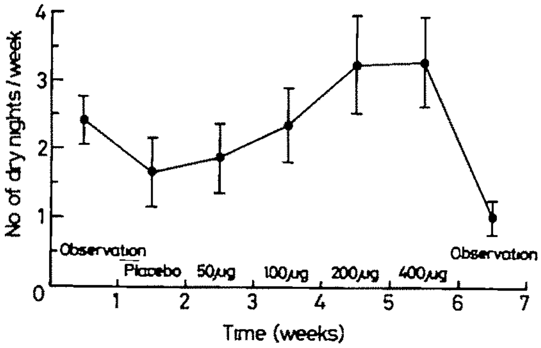

Fig. 1 *The response to single increasing doses of desmopressin given orally to 15 enuretic children*

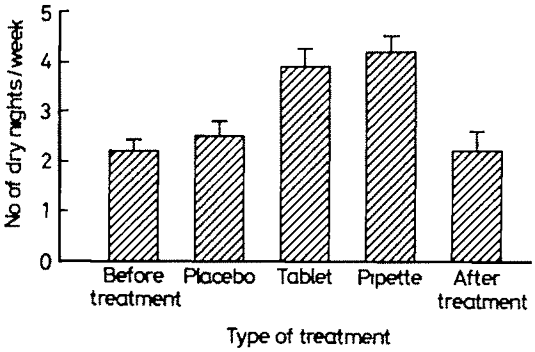

Fig 2 *No of dry nights a week after placebo, intranasal (20 µg) and oral (200 µg) desmopressin in 29 enuretic children*

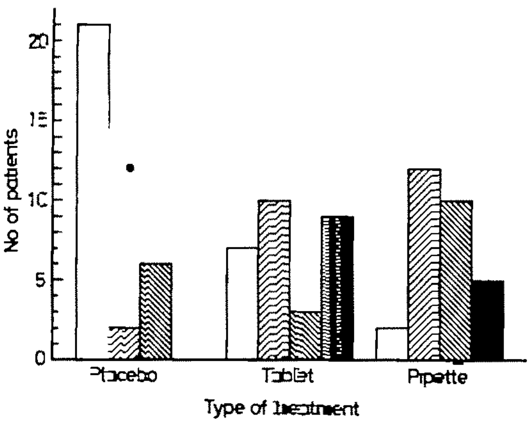

Fig. 3 *Graded response to placebo, intranasal, and oral desmopressin expressed as a percentage of the pretreatment response in 29 enuretic children.* ☐ *0–24%;* ▨ *25–49%,* ▧ *50–74%,* ■ *75–100% improvement*

Table *Response to treatment with desmopressin and urine osmolality measured in specimen taken at 5 00 am*

| *Urine osmolality (mOsm/kg)* | *No remaining dry* | *No who greatly improved* | *No who slightly improved* | *No with no improvement* |
|---|---|---|---|---|
| >1000 | 7 | 9 | 4 | 2 |
| > 800–1000 | 0 | 4 | 0 | 1 |
| > 600–800 | 0 | 0 | 1 | 0 |
| < 600 | 0 | 0 | 0 | 1 |
| Total | 7 | 13 | 5 | 4 |

Greatly improved=only one or two wet nights a week, slightly improved=one or more dry nights a week compared with placebo, no improvement=no change from placebo

Measurements of urine osmolality were higher during intranasal and oral treatment with desmopressin, but not significantly different from the measurements before treatment, or when the placebo was being taken. When patients were graded by response and stratified by measurements of urine osmolality, however, there was a clear and significant relation between the clinical response and the osmotic concentration of morning urine (Table). The best results were obtained in patients who had osmolality measurements of over 1000 mOsm/kg. Three patients had decreased serum concentrations of sodium (to 125–130 mmol/l) during treatment, but these returned to normal when desmopressin was stopped. The mean values were not significantly different throughout the study, and body weight was steady during the eight weeks. One patient had a low concentration of sodium in the serum before treatment and when the placebo was being taken, which may indicate polydipsia. There were no changes throughout the trial in concentrations of albumin or creatinine in serum, or in blood pressure readings.

No significant adverse effects were registered, but some patients complained of occasional nasal discomfort (n=2) and epistaxis (n=3); no difference was found between placebo and desmopressin treatment

## Discussion

The results of this study confirm the efficacy of desmopressin in the treatment of nocturnal enuresis and show that a single oral dose of 200 μg was as effective as a 20 μg dose given intranasally. Until recently the value of giving polypeptides orally was underestimated because it was thought that they were hydrolysed before reaching the absorption sites in the gastrointestinal tract. During the past two decades, however, oral absorption of dipeptides and tri-peptides has been shown.[9, 10] Furthermore, studies performed in rats, dogs, and man have shown that vasopressin, its analogues, and desmopressin in particular may all be absorbed when taken orally.[11] More recently, several studies have reported that long term treatment with desmopressin taken orally is both safe and effective in adults[5, 12] and children[6, 7] with diabetes insipidus Usually doses 10 to 20 times larger are needed for oral treatment, and patients with diabetes insipidus respond better taking three doses a day rather than two.

Several studies have shown significantly better results when desmopressin given intranasally in different doses was compared with placebo.[1–3, 13, 14] The drug works quickly, but relapses are common after treatment has finished. In our study nine patients (31%) remained dry after treatment, the others relapsed immediately. The mean number of dry nights a week after treatment in those that relapsed was 1·2 (0·3), which was noticeably worse than the mean during the observation week of 1·9 (0·3), or that observed when they were taking the placebo of 2·3 (0·3) ($p<0{\cdot}05$). This shows that there is a large percentage of patients who respond well to treatment, and even an observation period or waiting list for treatment will produce an improvement. Once treatment is over, however, most relapse immediately, and probably are closer to a real enuretic state than during the period before treatment.

The effect seems to be dose related, but in general the 20 μg dose given intranasally is used independently of age and body weight. In a recent study in 10 children with diabetes insipidus 10 μg given intranasally was equivalent to 200 μg given orally, and 20 µg given intranasally was equivalent to 400 µg given orally.[8] We decided to compare the 20 µg intranasal dose with the 200 µg oral dose, which we found in a pilot study to be as effective as a 400 µg dose, but with less effect on serum electrolytes and body weight.

The mechanism of action of desmopressin in nocturnal enuresis has been widely discussed Birkasova[1] postulated that it worked through its antidiuretic effect. Wille[15] and, more recently, Dimson[16] found significant positive correlations between morning urine osmolality and clinical response during treatment with desmopressin given intranasally. Our results confirm these findings Furthermore, these results suggest that the efficacy of desmopressin is related to its ability to raise overnight urinary osmotic concentration by increasing water reabsorption, and so reducing the diuresis and the volume of urine entering the bladder.

One of the many theories about the pathogenesis of enuresis is that enuretics may lack a nocturnal rise in secretion of endogenous vasopressin. George *et al*[17] were the first to describe a diurnal rhythm of vasopressin in normal adults which reached appreciably higher concentrations at night In two uncontrolled studies Nørgaard *et al*[18] and Puri[19] showed that vasopressin secretion in enuretic children failed to increase at night, one of the reasons for involuntary nocturnal micturition, therefore, may be nocturnal polyuria, which causes urine production to exceed bladder capacity. If this finding is substantiated by further controlled studies desmopressin may be a useful substitute for nocturnal vasopressin for patients with enuresis compounded by nocturnal polyuria.

Desmopressin given either nasally or orally can be used safely and effectively for most enuretic children; it is especially useful for those spending nights away from home Relapses after stopping treatment are common, however, but most patients considered desmopressin to be more effective than previous treatment, and the children were willing to continue treatment by either route.

We thank the nursing staff of the two paediatric departments, and Ferring AB, Malmo, Sweden, for the desmopressin tablets and pipettes

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# Five year prospective study of plasma renin activity and blood pressure in patients with longstanding reflux nephropathy

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SUMMARY Eight of 100 normotensive children who had pyelonephritic scarring secondary to urinary infection and vesicoureteric reflux were found in an earlier study to have increased plasma renin activity (PRA). Because the risk of these patients becoming hypertensive is between 10% and 20% and because renin activity may play a part in the pathogenesis of the hypertension, PRA and blood pressure were studied in 98 of the original group after five years of follow up. Two patients could not be traced, and other factors that might influence blood pressure or PRA led us to exclude 13 others, 10 of whom were girls taking oral hormonal contraceptives.

Increased PRA was found in 11 of the remaining 85 patients but not in five of the eight patients with increased PRA in the first study. Of eight children identified as hypertensive in the follow up study, only three had had increased PRA five years previously.

In normal children PRA decreases with age. In the initial study this tendency was less pronounced in children with renal scars, and in the follow up study it was reversed. This was also confirmed by PRA standard deviation scores, which showed a significant increase in PRA during the five years. PRA tends to rise in patients with pyelonephritic scars as they grow older.

There was no direct correlation between blood pressure and PRA, plasma creatinine concentration, or degree of scarring. Analysis of blood pressure standard deviation scores, however suggested an excessive rise in blood pressure during the five years.

Pyelonephritic scarring is a major cause of sustained hypertension in childhood.[1-3] This type of renal scar is produced by ascending urinary tract infection in the presence of vesicoureteric reflux early in childhood and has been called reflux nephropathy.[4-6] Once scarring is present in a child's kidney there is at least a 10% risk of subsequent hypertension.[7 8] Furthermore, there is an association between such hypertension and later deterioration in renal function. Early detection and treatment of hypertension in these patients are therefore important because of the high risk of morbidity and mortality.[9]

The aetiology of the hypertension has been difficult to establish because it is a late sequel of the scarring.[8 10] The renin-angiotensin system has been implicated[11 12] and we previously showed that plasma renin activity (PRA) is often increased in children with renal scars.[13 14] In 1978 we measured PRA in 100 normotensive children known to have renal scars and vesicoureteric reflux.[13] Eight had increased PRA (Fig. 1), and the natural tendency of PRA to fall with age was less pronounced than in normal controls (Fig. 2). That initial study supported the hypothesis that in children with scarred kidneys the renin-angiotensin system was over active and increased PRA might precede a rise in blood pressure. The present follow up study was done to reassess the relation between PRA and blood pressure in the same children after five years and to find out whether PRA predicts subsequent hypertension.

## Patients and methods

One hundred children with renal scarring visible in *x*-ray pictures and vesicoureteric reflux that had been corrected surgically were studied in 1978; for this study we traced 98 of these patients. Initially

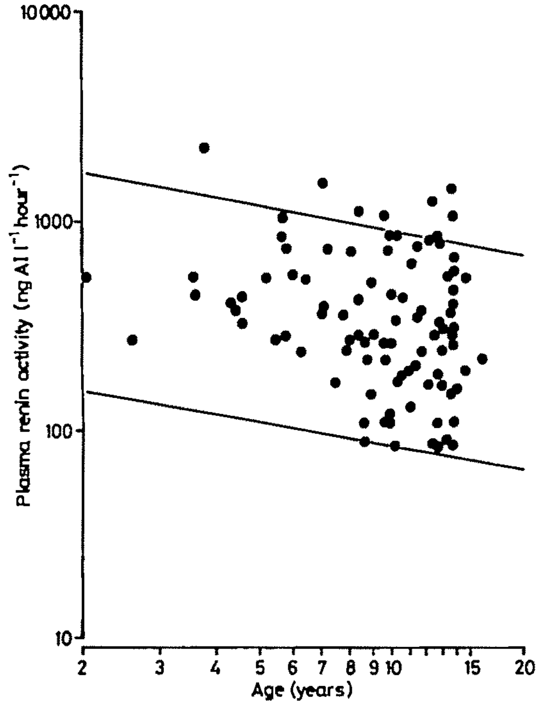

Fig. 1 *PRA in normotensive children with scarred kidneys in 1978 (Traditional units to SI angiotensin I 1297 ng/l=1 nmol/l).*

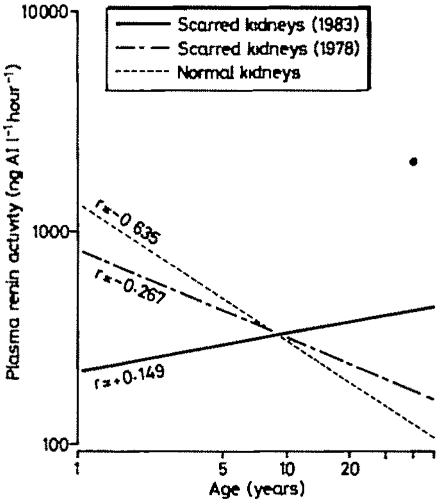

Fig 2 *Regression of PRA with age for children with normal kidneys and those with scarring in 1978 and 1983 (Traditional units to SI angiotensin I· 1297 ng/l=1 nmol/l)*

these children had normal plasma creatinine concentrations and blood pressure New factors likely to influence blood pressure or PRA were sought, and, although all patients were investigated, only 85 are included in this study: 13 patients were excluded because they were taking a hormonal contraceptive pill (n=10), were pregnant (n=1), had had a nephrectomy (n=1), or had died (n=1). Thus 36 male patients aged 7–21 years and 49 female patients aged 6–20 years were followed up.

The degree of renal scarring was reassessed from the most recent *x*-ray pictures available and scored as in the original study—that is, normal kidney=0, single small polar scar=1, complete polar destruction=2, loss of both renal poles or a small shrunken kidney=3. Scarring had increased in two patients, but this may have been due to a change in the imaging method used, from intravenous urography to scanning with dimercaptosuccinic acid labelled with technetium-99m. Neither patient had increased blood pressure or PRA.

Each child was asked to attend hospital, where blood pressure was measured in the supine and erect positions with a Dinamapp Vital Signs Monitor with an automatic tracer designed to eliminate observer bias. A 1 ml sample of blood was taken from the patients after they had rested supine for two hours PRA was estimated with a semimicro radioimmunoassay[15] and plasma creatinine concentration by the Jaffe reaction with an autoanalyser Because of the difficulty of comparing sodium excretion rates in children of different sizes, a urinary sodium· creatinine ratio was used as a convenient approximation. A urine sample was therefore obtained from each child, and mean sodium excretion was calculated from the sodium:creatinine ratio, assuming normal daily creatinine excretion to be constant at 132 mmol/kg body weight/24 h mean sodium excretion=urine sodium concentration/urine creatinine concentration.

## Results

In this follow up study PRA was increased in 11 (13%) of the 85 patients studied (Fig. 3) In the initial study eight of the 100 children had had increased PRA, but only three children showed high activity in both studies

In the 85 children followed up there was a positive correlation of PRA with age (r=+0·1486), the opposite of the negative correlation described in normal children (r=−0·635). In our original study we showed that in children with scarred kidneys this normal negative correlation was weakened (r=−0·267)[13]; after five years it was reversed (Fig. 2).

So that we could compare PRA in the children studied in 1978 and 1983 standard deviation scores

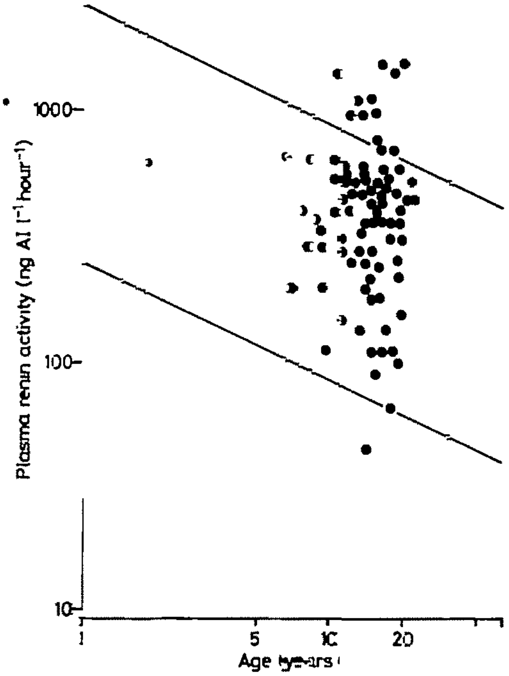

Fig 3 *PRA in children with scarred kidneys after five years in 1983 (Traditional units to SI: angiotensin I. 1297 ng/l=1 nmol/l).*

were calculated and compared with paired Student's *t* test. There was a significant increase ($p<0·001$) in the standard deviation scores between the initial study and the follow up study (Table 1).

In the follow up study we found no significant relation between PRA and mean sodium excretion, plasma creatinine concentration, or the degree of renal scarring (Table 2). There was no difference in mean sodium excretion between the children studied and a group of healthy children evaluated to establish normal values for PRA. Of the 11 patients with abnormally increased PRA, none had a raised plasma creatinine concentration, whereas five of the remaining 74 subjects did. The degrees of scarring in the 11 children scored between 2 and 6 on the scoring system described (Table 2).

Table 1 *Comparison of PRA and blood pressure measurements taken five years apart in 85 patients with renal scarring*

| *Measurement* | *Statistical method* | *p value* | *Conclusion* |
|---|---|---|---|
| PRA | Paired *t* test on SD scores | <0·001 | Highly significant increase |
| Diastolic blood pressure | Paired *t* test on SD scores | <0·001 | Highly significant increase |
| Systolic blood pressure | Paired *t* test on SD scores | <0·05 | Significant increase |

Table 2 *Details of patients with raised PRA at five year follow up*

| *PRA ng AI $l^{-1}$ $h^{-1}$ (nmol AI $l^{-1}$ $h^{-1}$)* | | *Degree of scarring* | *Plasma creatinine (μmol/l)* | *Age (years)* |
|---|---|---|---|---|
| *Patients values* | *Upper limit of normal* | | | |
| 1338 (1·03) | 880 (0·67) | 6 | 74 | 10·7 |
| 943 (0·73) | 790 (0·60) | 2 | 44 | 12·3 |
| 965 (0·74) | 770 (0·59) | 4 | 74 | 13·5 |
| 1075 (0·83) | 770 (0·59) | 2 | 64 | 13·6 |
| 1009 (0·78) | 750 (0·58) | 5 | 87 | 14·9 |
| 746 (0·58) | 746 (0·57) | 4 | 77 | 15·4 |
| 965 (0·74) | 725 (0·55) | 4 | 44 | 15·8 |
| 1491 (1·15) | 710 (0·54) | 2 | 83 | 16·2 |
| 690 (0·53) | 680 (0·52) | 2 | 57 | 17·7 |
| 1404 (1·08) | 670 (0·51) | 5 | 87 | 18·3 |
| 1491 (1·15) | 660 (0·50) | 2 | 68 | 19·5 |

Values given as traditional (SI) units

Hypertensive patients were excluded from the initial study. At follow up blood pressure was above the 95th centile in three, none of whom had increased PRA. A further four patients had borderline increases in blood pressure at the 90th centile for their ages. Three of these four had had increased PRA during the initial study, but in only one was the activity high after five years. Centiles of blood pressure were based on American Task Force figures.[16]

As for PRA, standard deviation scores were calculated for both systolic and diastolic blood pressures and the scores in 1978 and 1983 compared. The difference between systolic blood pressure scores was significant ($p<0·05$), but there was a more obvious difference in those for diastolic blood pressure ($p<0·001$) (Table 1). There was no significant correlation between blood pressure and PRA, plasma creatinine concentration, or degree of scarring (Spearman's rank correlation test). These findings are similar to those of the previous study.

Two subjects had increased PRA in both studies, and their blood pressure lay well within the normal range on both occasions. The one patient who died between the two studies had hypertensive encephalopathy, he had normal blood pressure and PRA but grade 5 renal scarring in the initial study.

## Discussion

The hypothesis that renin plays a major part in the hypertension associated with pyelonephritic renal scarring was supported by our earlier observation of a high incidence of increased PRA in children in whom both were found.[13] [14] When we detected increased PRA in eight of 100 normotensive children with renal scars we postulated that this increase in PRA might predate, and so predict, the development of hypertension in these patients. The risk of subsequent hypertension has been estimated as being between 10% and 20%,[8] and there is often a long delay between scarring and an obvious rise in blood pressure. We therefore followed up these children as they grew up After five years four of the original patients were seriously hypertensive and four others had borderline hypertension, confirming that we identified an abnormal population because 11 hypertensive children were excluded from the initial study.

The follow up data at five years do not confirm that a single random measurement of PRA can detect abnormal PRA sufficient to predict the risk of hypertension. Only three of eight children with increased PRA initially had increased PRA at five year follow up; one of these was hypertensive. Eight children with increased PRA at follow up had had normal PRA when first studied Thus the number of patients with high PRA increased to a total of 16, confirming that pyelonephritic patients are likely to develop increased PRA.

The comparison of standard deviation scores for PRA between the children studied in 1978 and those studied in 1983 confirm that there was a significant increase in the scores during the five years. This observation, coupled with the development of a positive correlation between PRA and age during the five years in our patients with renal scarring, is particularly important. These findings confirm that the normal tendency of PRA to fall with age is reversed; they also confirm the role of renin in pyelonephritic hypertension and may explain the delay in onset.

It seems, however, that PRA does not necessarily lie above the normal range in all patients at risk of hypertension and that the activity may fluctuate even under standardised conditions in individual patients. This may be explained by the second pressor effect of angiotensin described by Dickinson and Lawrence.[17] They showed in animal studies that angiotensin II given in doses too small to produce an appreciable rise in blood pressure, when given by single injection, can cause sustained hypertension when given as a prolonged infusion. A similar mechanism may cause hypertension in those subjects who become hypertensive despite having apparently normal PRA. Their PRA may be higher than it was before the kidneys were damaged, so producing this second pressor effect. The effect of PRA on blood pressure is most obvious when the activity is consistently above the normal range for age, but we suggest that hypertension may also be caused over a long time span by smaller or fluctuating increases. Repeated measurements of PRA and a longer period of study are required to evaluate this hypothesis.

Measuring PRA under different conditions—for example, with the patient standing or when sodium is repleted—might accentuate changes in individual patients Because it would be difficult to standardise conditions of sampling we used only samples taken from supine, unstimulated patients.

Several factors probably interact with renin in individual patients to determine their blood pressure. For example, those whose blood pressure is naturally high are most at risk of a cumulative effect. We found that the blood pressure standard deviation scores, both for systolic and diastolic pressures, increased during the five year follow up This points to a greater increase in blood pressure in this group of patients than might be expected with time, which may be related to the underlying renal disease and renin activity.

The amount of damage to the kidneys may not be completely shown by radiological examination. When renal tissue is lost a hyperfiltration phenomenon[18 19] in the remaining nephrons may lead to deteriorating function, and a local immunological reaction to scarred tissue may have a similar effect. If these factors were relevant an important association between blood pressure and the degree of scarring or the incidence of proteinuria might be expected. We did not identify such associations, but a further prospective study is planned.

The oral contraceptive pill affects the renin-angiotensin system.[20] Of 10 patients taking the pill (Table 3), three had increased PRA; all these girls were excluded from our analysis. The hypertensive risk from renal scarring and from taking oestrogen is probably cumulative, and the pill may not be the ideal method of contraception for patients with chronic pyelonephritis.

This prospective study of subjects with reflux nephropathy confirms that the renin-angiotensin

Table 3 *PRA in patients taking oral contraceptives*

| *Age of patient (years)* | *PRA ng AI $l^{-1}$ $h^{-1}$ (nmol AI $l^{-1}$ $h^{-1}$* | *Upper limit of normal for age* |
|---|---|---|
| 16 7 | 110 (0 08) | 700 (0 54 |
| 16 9 | 439 (0 33) | 700 (0 54 |
| 17 2 | 768 (0 59) | 690 (0 53 |
| 18 36 | 241 (0 18) | 670 (0 52 |
| 18 76 | 439 (0 33) | 670 (0 52 |
| 18 8 | 1513* (1 16) | 670 (0 52 |
| 19 1 | 329 (0 25) | 660 (0 51 |
| 19 3 | 176 (0 13) | 660 (0 51 |
| 19 43 | 285 (0 21) | 660 (0 51 |
| 20 0 | 877* (0 67) | 650 (0 50 |

*Abnormally high for age

system is disturbed after renal scarring. This is most dramatically shown by the reversal of the natural tendency of PRA to fall with age and by a significant increase in PRA standard deviation scores during the five years of follow up These were paralleled by an increase in the blood pressure standard deviation scores during the same period. We propose to continue the longitudinal follow up to determine the total incidence of hypertension and to evaluate other factors that may be operating in hypertensive patients in whom the renin-angiotensin system seems normal. Further study may also identify the factors that have a role in the deterioration in renal function and may explain the influence of oral contraceptives on blood pressure in these subjects.

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# Adrenal cortical tumours: epidemiological and familial aspects

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SUMMARY Epidemiological data on the 14 cases of adrenal cortical tumour registered with the Manchester Children's Tumour Registry from 1954 and 1985 are presented. The incidence of adrenal cortical carcinomas was 0·3%, mainly in girls, most of whom presented with virilisation. The incidence of neoplastic disease among close relatives was ascertained, but, except in siblings, this was not significantly higher than would be expected. Evidence from extended pedigrees, however, indicates that at least four of the children could be members of families with the SBLA (sarcoma, breast and brain tumour, leukaemia, laryngeal and lung cancer, and adrenal cortical carcinoma) cancer family syndrome, and that other relatives may be at risk of developing such neoplasms.

Adrenal cortical tumours are rare in children, the incidence of adrenal cortical carcinoma being estimated as 0·2% of all childhood malignancies[1] In spite of this there have been several reports of associations between adrenal cortical tumours and certain congenital malformations and growth disorders, such as hemihypertrophy, Beckwith-Wiedemann syndrome, and malformations of the urinary tract.[2 3] Adrenal carcinoma has also been reported in patients with Gardner's syndrome.[4] Adrenal cortical carcinoma may also predispose to second malignancies, and survivors may later develop brain tumours,[2] melanoma,[5] and certain tumours induced by radiation—for example, osteogenic sarcoma[2] and renal cell carcinoma.[6]

Adrenal cortical tumours are known to be part of a familial syndrome including sarcomas, brain tumours, breast cancer and leukaemias. In one family described by Kenny *et al*,[7] the father and sister of an affected child developed 'bone tumours' at the ages of 29 and 9, respectively. In another family the mother and maternal aunt both had breast cancer diagnosed in their 30s, while a maternal uncle had a brain tumour at the age of 39, and a maternal cousin also developed an adrenal tumour in infancy[7] The occurrence of bilateral breast cancer in the mother of two siblings with adrenal cortical carcinoma was reported by Shimke.[8]

In an extensive family described by Lynch *et al* there were two adrenal cortical tumours, one in a man aged 23, and one in a girl of 3.[9] Li and Fraumeni previously reported the association between soft tissue sarcoma in childhood and the early onset of breast cancer in the mothers of these children.[10] Both of the first two such families reported in England by Pearson *et al* included a child with adrenal cortical carcinoma.[11]

In the report by Kenny *et al*, of seven cases of virilising adrenal cortical tumour, four of the seven cases had a notable family history of malignancy.[7] Most families with the sarcoma, breast and brain tumour, leukaemia, laryngeal and lung cancer and adrenal cortical carcinoma (SBLA cancer family) syndrome reported so far, however, have been selectively documented, usually because of cases of cancer in other family members. To what extent the occurrence of an adrenal cortical tumour in an individual indicates that he or she is part of a 'cancer family' is not known. The aim of this paper is to present epidemiological data about the incidence of adrenal cortical tumours in a population based series, and to shed light on the association between other neoplasms and adrenal cortical tumours: surveillance programmes for early detection of cancers in relatives may thus be more effectively deployed.

## Methods

All cases of adrenal cortical tumour in the Manchester Children's Tumour Registry diagnosed between

1 January 1954 and 31 December 1985 were included in the study. The Manchester Children's Tumour Registry was described in detail by Birch *et al*,[12] and it was estimated to be 95–98% complete.[13] The histology slides of all cases were reviewed to confirm the diagnosis.

The following information was abstracted from the records of each child included in the study: sex, age at diagnosis, side of the tumour, presenting symptoms, congenital abnormalities and other medical history, and, where available, family history of cancer.

The current general practitioners of both parents of each child were then identified with the help of family practitioner committees, the National Health Service central register and other local sources. These methods were described by Birch *et al*.[14] The general practitioners were then given details of the study and asked for permission to approach the family for interview. This was usually done by letter, but in the case of children who were still attending for follow up the hospital consultant's permission was sought and the parents contacted at their next visit to the clinic.

Parents were usually interviewed at home. They were asked about the child's medical history, including congenital abnormalities, serious acute and chronic illnesses, and operations. Similar details were obtained for all first degree relatives—that is parents and siblings. Reports of serious malformations and neoplasms were recorded for all second degree relatives, and for third degree and more distant relatives when possible. Dates of birth or ages of all first and second degree relatives were obtained so that relative risk ratios for the development of malignancies could be calculated. In addition, parents were asked about occupational exposures to chemicals and radiation before the birth of the index child To obtain consistent information from parents, check lists of diseases and substances were used.

Reports of all serious medical conditions in the child were confirmed from hospital records or by correspondence with general practitioners. We tried to confirm reports of all neoplastic conditions in relatives by reference to hospital notes, the appropriate regional cancer registry, questionnaires to general practitioners, or from copies of death certificates. Where possible the histological slides were reviewed. If parents or siblings had died before the interview the cause of death was confirmed from medical records.

The cumulative risks of developing cancer at a particular age were estimated for all first and second degree relatives using data from the North West region.[15] These were used to calculate the expected numbers of cancers among these relatives, taking into account their age at the time of interview, or at death, as appropriate The method described by Rothman and Boice for exact testing and estimation of a Poisson variate was used to test whether the observed numbers of cancers were greater than expected.[16]

## Results

There were 12 boys and two girls with adrenal cortical tumours between 1954–85 who were registered with the Manchester Children's Tumour Registry. Four of the tumours were classified as adenomas, the rest being carcinomas. For the 30 years for which population data are available, this represents an incidence of adrenal cortical tumours of about 1 in 500 000 in boys, 1 in 87 000 in girls, or 1 in 150 000 overall. Adrenal cortical carcinomas in this series comprised 0·3% of all childhood malignancies registered with the Manchester Children's Tumour Registry.

Age at diagnosis ranged from 8 months to 12 years 7 months (median 3 years 9 months). Most of the children presented with precocious sexual development with virilisation. Six cases also had Cushing's syndrome, but abdominal pain or mass was the only presenting symptom in two of the girls The adenomas ranged from 3–6 cm in diameter, and the carcinomas from 8–25 cm

All patients were treated by surgery, and some had radiotherapy either postoperatively or for recurrent disease. Five children were treated by chemotherapy for recurrences. Table 1 gives details of all the cases, together with presenting symptoms, treatment, and outcome. Cases 1, 2, 7, and 13 have previously been described by Stewart *et al*,[17] and case 4 by Pearson *et al*[11]

Thirteen families were interviewed, and the remaining set of parents completed a postal questionnaire. Both parents were seen in only three cases, two mothers and two fathers were already dead and four sets of parents were divorced. In cases where the mothers had died the interview was carried out with the father in one case, and with the maternal grandparents in the other.

**Medical History of the children and their relatives.** All the children were born at full term except case 4 (37 weeks) and case 5 (33 weeks because of maternal diabetes and hypertension). Delivery was normal or by forceps except for case 5, who was born by caesarean section. Birth weights were available for 13 cases and ranged from 1600 g (case 5) to 4800 g (mean 3500 g, median 3800 g) The ages of the mothers at the birth of the child ranged from 23 to

39 years (mean 28 years 10 months, median 31 years 6 months). Six mothers and eight fathers were 30 years or over at the birth of the child

Table 2 shows the congenital abnormalities in the children, their parents, and siblings, and Table 3 lists other conditions Other conditions in second and higher degree relatives included hypercholesterolaemia (maternal aunt of case 7); pernicious anaemia (paternal aunt of case 3); possible velo-cardio-facial syndrome (maternal aunt of case 8); sebaceous cysts (maternal grandmother of case 6) and a major congenital heart abnormality (maternal first cousin of case 14).

**Exposure to potentially toxic substances.** Information on parental exposure to such substances was difficult to obtain, but four mothers and seven fathers had been exposed to various dusts and chemicals before or during the index pregnancy. These included cotton and wool dusts, solvents, tar, chemicals, insulation materials, dyes and possibly fertilisers. One father had been a chemical process worker before the child's birth, and three parents—including both the mother and father of case 13—had worked in the rubber industry.

**Cancers in first and second degree relatives.** Table 4 shows the observed and expected numbers of cancers in first degree relatives, and in those second degree relatives for whom information was obtained. The mother of case 4 developed infiltrating duct carcinoma of the breast at the age of 27, and the father of case 11 died of a brain tumour, probably a glioma, at the age of 35. Information on 20 brothers and 16 sisters was available, and only one had developed a malignancy; the brother of case 4 developed a dense, poorly differentiated rhabdomyosarcoma of the middle ear at the age of 19

Table 1 *Adrenal cortical tumours in the Manchester Children's Tumour Registry 1954–1985*

| *Case No* | *Sex* | *Diagnosis* | *Age at diagnosis (months)* | *Symptoms* | *Initial treatment* | *Outcome and survival* |
|---|---|---|---|---|---|---|
| 1 | Female | Left carcinoma | 8 | Virilisation, acne, Cushing's syndrome | Surgery and radiotherapy | Alive (14 years) |
| 2 | Female | Right carcinoma | 10 | Virilisation, precocious development, abdominal mass | Surgery and radiotherapy | Alive (19 years) |
| 3 | Female | Right carcinoma | 16 | Virilisation | Surgery and radiotherapy | Alive (11 years) |
| 4 | Female | Left adenoma | 17 | Virilisation, acne | Surgery | Alive (6 years) |
| 5 | Female | Right carcinoma | 34 | Virilisation, acne abdominal mass | Surgery and radiotherapy | Alive (10 months) |
| 6 | Female | Left carcinoma | 36 | Virilisation, Cushing's syndrome, acne | Surgery and radiotherapy | Dead (27 months) |
| 7 | Female | Left adenoma | 38 | Virilisation, Cushing's syndrome, precocious development | Surgery | Alive (24 years) |
| 8 | Female | Right carcinoma | 52 | Abdominal pain, mass | Surgery and radiotherapy | Dead (20 months) |
| 9 | Female | Right adenoma | 66 | Virilisation, acne, precocious development | Surgery | Alive (7 years) |
| 10 | Male | Left adenoma | 95 | Precocious puberty | Surgery | Alive (5 years) |
| 11 | Female | Right carcinoma | 110 | Abdominal pain | Surgery and radiotherapy | Dead (9 months) |
| 12 | Female | Left carcinoma | 126 | Cushing's syndrome | Surgery | Dead (3 weeks) |
| 13 | Male | Left carcinoma | 140 | Cushing's syndrome, abdominal pain | Surgery | Dead (8 months) |
| 14 | Female | Left carcinoma | 151 | Virilisation, Cushing's syndrome | Surgery and radiotherapy | Dead (10 months) |

Table 2 *Congenital abnormalities in case children, parents, and siblings*

| *Case No* | *Child* | *Parents* | *Siblings* |
|---|---|---|---|
| 2 | Haemangioma left shoulder | | — |
| 3 | Small white patch on leg | | — |
| 5 | Head circumference just below 90th centile | | — |
| 6 | Two small brown patches on abdomen and foot | | — |
| 7 | | Brown mark on chest (mother) | Brown mark on leg (sister) |
| 8 | | | Spastic and mentally retarded, squint and ocular hypertelorism, epicanthic folds (brother) |
| 10 | Slight right hemihypertrophy | Bifid left renal pelvis and duplication of ureter in its upper quarter (mother) | |
| 13 | | | Bilateral talipes equino varus (brother) |

Table 3 *Other non-neoplastic conditions in case children, parents, and siblings*

| *Case No* | *Child* | *Mother* | *Father* | *Siblings* |
|---|---|---|---|---|
| 2 | Corneal opacity, pelvic exostoses (post-irradiation) | Corneal opacity | | Neonatal death (brother), corneal opacities (brothers) |
| 4 | | Ovarian cyst | | |
| 5 | | 2 miscarriages, insulin-dependent diabetic from 14 years of age | | |
| 6 | | 1 miscarriage, sebaceous cysts on scalp, mastitis left breast | | |
| 7 | | | Tuberculosis | Endometriosis (sister) |
| 8 | | | Gastric ulcer | Exostosis distal femoral shaft (sister) |
| 9 | | Fimbrial ovarian cyst, breast cysts | | |
| 10 | Polycythaemia and splenomegaly, at the age of 3 | Poliomyelitis | | Neonatal death (sister) |
| 11 | | | Bilateral Dupuytren's contractures of third fingers | |
| 12 | | 3 miscarriages including twin pregnancy | Kidney stones | |
| 13 | Cretinism bilateral inguinal herniae | Died cerebral embolism, Mitral valve disease | | Gastric ulcer (brother) |
| 14 | Psoriasis | | | |

Table 4 *Cancer risk in first and second degree relatives of children with adrenal cortical tumours*

| | *Total No* | *Observed No* | *Expected No* | *Relative risk* | *p value* |
|---|---|---|---|---|---|
| Mother | 14 | 1 | 0·58 | 1·7 | 0·28 |
| Father | 14 | 1 | 0·78 | 1·3 | 0·36 |
| Brothers | 20 | 1 | 0·07 | 14·3 | 0·035 |
| Sisters | 16 | 0 | 0·07 | — | 0·53 |
| Grandfathers | 24 | 4 | 3·8 | 0·9 | 0·43 |
| Grandmothers | 26 | 4 | 4·4 | 0·9 | 0·54 |
| Aunts | 37 | 1 | 2·3 | 0·4 | 0·78 |
| Uncles | 40 | 2 | 2·6 | 0·8 | 0·61 |

months. The maximum age of the siblings, however, was only 28 years.

Four grandfathers had confirmed cancer. These included carcinoma of stomach at the age of 76 (maternal grandfather of case 11), carcinoma of prostate at the age of 70 (paternal grandfather of case 11); carcinoma of lung at the age of 65 (paternal grandfather of case 14), and a brain tumour at the age of 35 (paternal grandfather of case 5). Three grandmothers also had cancer. The maternal grandmother of case 9 had a double primary tumour—a carcinoma of cervix at the age of 54 and a carcinoma of breast at the age of 65. The maternal grandmother of case 3 also had breast cancer at the age of 47, and the maternal grandmother of case 11 died of a malignant melanoma of the forearm at the age of 70. Only one aunt was reported as having died of cancer; the maternal aunt of case 13 had breast cancer at the age of 50, but this was an unconfirmed diagnosis. Two uncles died of lung cancer (paternal uncle of case 7 at the age of 70, and the maternal uncle of case 13, at the age of 56). None of these groups of relatives other than the brothers showed a pronounced excess of malignancies.

Benign neoplastic disease was also confirmed in three patients: case 2, who had a congenital haemangioma, subsequently developed a lipoma on the left lower chest; the mother of case 6 also had a lipoma removed from the left axilla at the age of 28, and the paternal cousin of case 14 had a fibroadenoma of the breast at the age of 15 years.

**Cancers in other family members.** Extended pedigrees relating to the child's third and higher degree relatives were available for only five of the 14 cases, although details of one or more lines of inheritance were given in two further families. With the exception of families 3, 4, and 5, the cancers confirmed in the known relatives were apparently unremarkable in their histological types and ages at onset, the only unusual neoplasm being a hydatidiform mole in a fourth degree relative of case 1.

The pedigree of case 4 has already been discussed in detail by Pearson *et al.*[11] This family shows features of the typical SBLA cancer family syndrome first described by Li and Fraumeni. soft tissue sarcoma and adrenal cortical tumour in two siblings, and early onset breast cancer in the mother. The mother's paternal grandmother also had breast cancer at the age of 64 and her paternal cousin had a seminoma diagnosed at the age of 23

The pedigree of case 3 is shown in the Figure. Although the parents. aunt, uncle, and cousins of this child are all well at the time of writing, there are clear indications that the SBLA cancer family syndrome has been inherited from the father's mother's family. The paternal grandmother de-

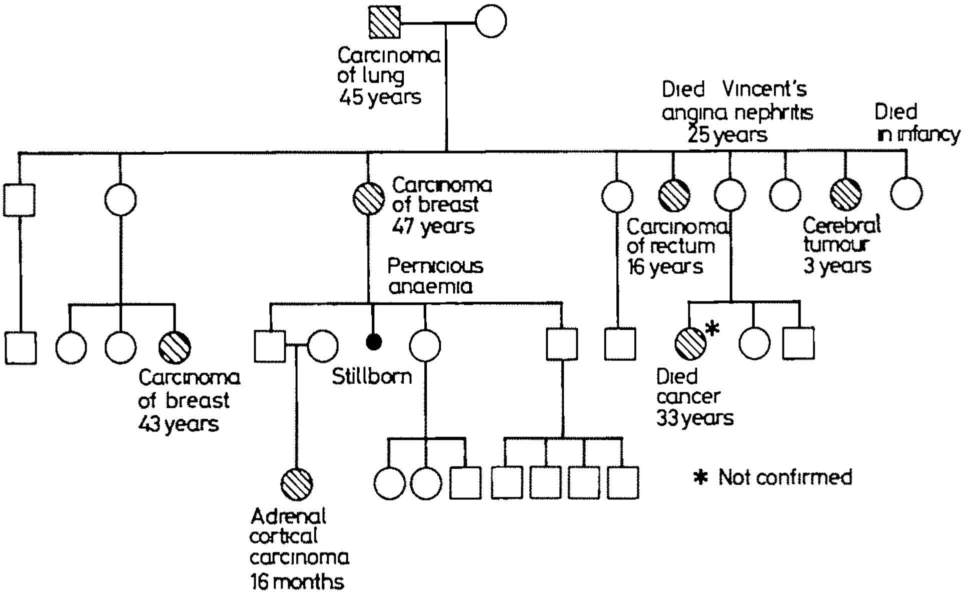
Carcinoma of lung 45 years
Died Vincent's angina nephritis 25 years
Died in infancy
Carcinoma of breast 47 years
Pernicious anaemia
Carcinoma of rectum 16 years
Cerebral tumour 3 years
Carcinoma of breast 43 years
Stillborn
Died cancer 33 years
* Not confirmed
Adrenal cortical carcinoma 16 months

Figure *Pedigree of case 3*

veloped carcinoma of the left breast at the age of 47 Death certificates of two of her sisters showed that one died of cancer of the rectum at the age of 16, and the other of a cerebral tumour at the age of 3 The father's cousin was treated for breast cancer at the age of 43, and another cousin is said to have died of cancer in her 30s The paternal grandmother's father died of lung cancer at the age of 45. In family 5 the paternal grandfather died at the age of 35 from a cerebral tumour. Further details of this side of the family are, unfortunately, not available.

**Second malignancies.** Eight of the children, including all those with adenomas, survived their initial neoplasm for periods ranging from 10 months to 24 years. Case 1, however, whose carcinoma was diagnosed at the early age of 8 months recently developed sarcoma of the left breast, which was induced by radiation, 13 years after surgery and radiotherapy. Another case, described by Stewart[17] but not included in this series, as she was living outside the North West area at the time of initial diagnosis, had an adrenal cortical carcinoma treated by excision and radiotherapy at the age of 18 months, and developed a chondrosarcoma of the fifth and sixth left ribs and a sclerosing osteogenic sarcoma of the sacrum 10 years after treatment.

## Discussion

The incidence of carcinomas in this series is similar to that previously reported,[1] and confirms the preponderance of girls noted in other series [18 19] Presenting symptoms were also similar to those previously reported, with most of the children showing virilisation. The tumours were almost equally distributed between the right and the left glands. Only two of the children were under the age of one year at diagnosis although some of the other cases were symptomatic up to a year or more before diagnosis.

Case 10 was the only child who had hemihypertrophy and whose tumour seemed, therefore, to be associated with a growth disorder syndrome. This case was one of only two boys in the series, and interestingly, although adrenal cortical tumours are generally more common in girls, the association between hemihypertrophy and adrenal cortical neoplasms seems to be more common among boys.[2] The mother of this child has anomalies of the renal tract, and three of her grandparents were reported to have died of cancer in old age—two of cancer of the bladder—but these were not confirmed. The child himself developed polycythaemia at the age of 3. This condition has been reported as a rare manifestation of adrenal cortical lesions,[20] and perhaps this was the first symptom of his tumour.

The presence of corneal opacities in case 2 and her mother and siblings raises the possibility that this family may have neurofibromatosis. Brown patches on the skin were reported in case 6, and in the mother of case 7 In none of these families, however, is there sufficient evidence to confirm this diagnosis.

The possibility of a brain disorder, similar to that reported by Fraumeni and Miller[2] in two cases in their series, is raised by the sibling of case 8 who is mentally retarded with alternating convergent squint, ocular hypertelorism, and epicanthic folds. The maternal grandmother of this case was investigated for possible raised intracranial pressure in her 20s, but no evidence of brain tumour was found.

There were no obvious cases of multiple endocrine neoplasia in the series, although case 13 was described as a cretin; the mother of case 5 suffered from diabetes mellitus; and one father and one sibling were said to have gastric ulcers In case 6 there is a slight possibility of Gardner's syndrome, with the occurrence of sebaceous cysts in both the mother and maternal grandmother.

Overall cancer risks in close relatives were not above expectation, except for the male siblings. The extended pedigrees, however, show that certain families exhibited features of the SBLA cancer family syndrome, in which susceptibility to cancer seems to be inherited in an autosomal dominant fashion. Family 4 was a clear example of this, and there was similar strong evidence in families 3, 5, and 11.

With the exception of case 10 who had hemihypertrophy, the remaining cases may be sporadic, but because extended pedigrees were not available in most of them, no conclusions can be drawn about any possible pattern of inheritance. Genetic susceptibility of a different kind may be indicated, however, by the presence of cutaneous lesions in certain cases and their relatives—for example, haemangioma, lipoma, and café au lait patches. All these manifestations were reported by Fraumeni and Miller in their series of adrenocortical neoplasms [2] One further point of interest is that the paternal uncle of case 7, who had oat cell carcinoma of the lung became heavily pigmented before his death, probably because of the melanin stimulating hormone produced by the tumour. Oat cell carcinoma of the lung is also associated with Cushing's syndrome, and this child who had Cushing's syndrome, and her uncle might have had a genetic defect in common.

In three of the four families who probably had the SBLA cancer family syndrome there was evidence of paternal inheritance of cancer susceptibility, so the occurrence of early onset breast cancer in only one of the mothers may be an underestimate of the risk for the mothers of children with adrenal cortical tumours as a whole, and a reflection of the small sample studied. In family 11 the presence of a brain tumour in the child's father and malignant melanoma in the maternal grandmother may indicate inheritance of susceptibility from both sides of the family in view of the reported association between adrenal cortical carcinoma and malignant melanoma.[5]

Three of the four cases with SBLA family cancer syndrome were under the median age at diagnosis, but apart from this there seems to be little, apart from a family history of neoplasia, which would indicate cancer risk in these children The occurrence of a second sarcoma induced by radiation in case 1, and of two such tumours in the additional case described, indicates that continued surveillance of the surviving cases is desirable, especially if radiotherapy has been part of their initial treatment Where a pattern of cancer compatible with a cancer family syndrome has been recognised, certain family members who are at present well must also be regarded as being at high risk of developing neoplastic disease characteristic of this syndrome, and they should be offered surveillance and, where appropriate, genetic counselling.

We thank Cora Christmas who traced the parents, the general practitioners who gave us permission to approach them for interview, and the staff of the National Health Service central register, Southport, and the family practitioner committees We also thank the pathologists who sent us material for review

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# Nosocomial hepatitis A infection in a paediatric intensive care unit

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SUMMARY Seven members of staff in a paediatric intensive care unit and two of their relatives developed hepatitis A over a period of five days. A 13 year old boy who was incontinent of faeces prior to his death, was presumed to be the source of infection. Two hundred and sixty seven other members of staff underwent serological testing and were given prophylactic pooled gamma globulin. Twenty three per cent were immune before exposure. Of people born in the United States, those at highest risk of developing the disease are physicians, dentists, nurses and those under the age of 40. Of those born outside the United States, being white and under the age of 30 are the two main risk factors. Data from a questionnaire sent to 19 nurses at risk (six cases, 13 controls) suggested that sharing food with patients or their families, drinking coffee, sharing cigarettes and eating in the nurses' office in the intensive care unit were associated with an increased incidence of hepatitis. Nurses with three or four of these habits were at particular risk. The costs of screening and prophylaxis were US$64·72 per employee, while prophylaxis alone would have cost US$8·42 per employee. Assessing risk factors on the one hand and costs of prophylaxis on the other are important elements in the control of nosocomial infections.

Hepatitis A usually spread through food, has recently been described as an important cause of nosocomial infection.[1 2] Several papers report its transmission by blood[3–5] or platelet[6] transfusion Although sometimes the mode of transmission is unknown,[7] a major source of cross contamination in hospitals may be the patient with diarrhoea whose hepatitis has not yet been diagnosed.[8–12] The patient discussed in this paper may have infected staff during the prodromal period while he was incontinent of faeces. This outbreak was studied to identify important risk factors among staff who acquired hepatitis A by comparing their demographic characteristics and the results of a questionnaire with similar data from exposed but uninfected staff at risk.

## The outbreak

In 1981 the paediatric intensive care unit at The New York Hospital comprised eight beds in two rooms staffed by 21 nurses. In early September there was an outbreak of hepatitis A, with nine primary and one secondary case.

On 3 September the department of epidemiology was advised that five intensive care nurses and the husband of one of them had developed hepatitis (Figure); three nurses were ill enough to require admission to hospital. The next day two of the inpatient nurses were reported as having positive titres of anti-hepatitis A virus (HAV) IgM which confirmed the diagnosis of hepatitis A. Two additional cases, a junior doctor and the sister of another nurse, were discovered All members of staff assigned to the intensive care unit and the adjacent general paediatric ward as well as patients in the unit, were considered to have been exposed. Following serological testing for serum glutamic pyruvic transaminase activity (SGPT) and titres of hepatitis B surface antigen ($HB_sAg$), and both anti-HAV and anti-HAV IgM for hepatitis A, each received inoculation with pooled gamma globulin as prophylaxis against hepatitis A. Pooled gamma globulin was also given to those closely associated both with patients and staff.

Sharing of food and drinks was forbidden. The paediatric intensive care unit was closed for four weeks following the last case and thoroughly

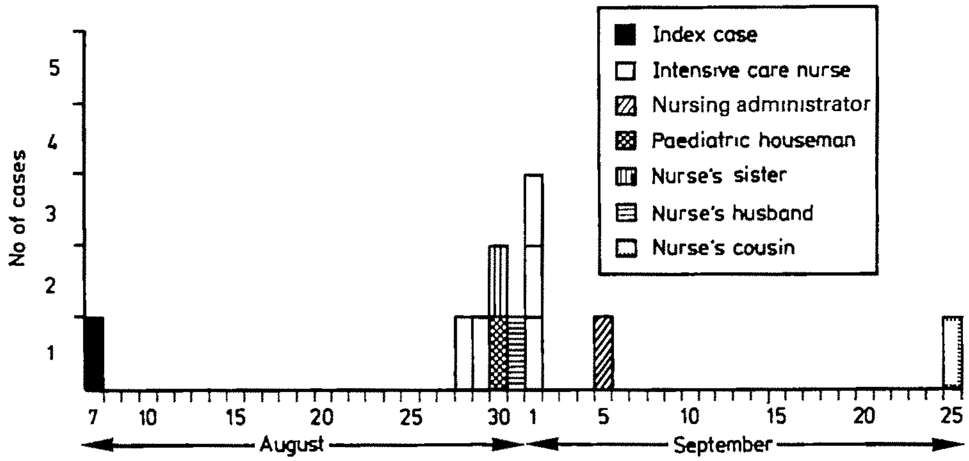

Figure *Epidemic curve of outbreak in paediatric intensive care unit*

cleaned. A temporary intensive care unit was set up immediately adjacent to it and patients were transferred there after their parents had given written informed consent, and they had received prophylactic pooled gamma globulin.

Abnormal SGPT activity was reported in an asymptomatic nursing administrator, but this was attributed to prophylaxis with isoniazid following a positive Mantoux test. After her anti-HAV IgM titre was reported positive she became symptomatic and was taken off duty, she was the last primary case.

The local health department knew of no other clusters of hepatitis A infection in the community. There were no other cases either in the adjacent paediatric unit or in the main hospital. As the cases occurred simultaneously and in the same place, investigation of this outbreak focused on a possible common source in the paediatric intensive care unit.

The incubation period for hepatitis A is 15 to 50 days (mean about 28 days)[13] and the period of exposure was between 12 July to 16 August As one infected nurse was on holiday from 21 July to 2 August and the infected couple (nurse and her husband) went on holiday on 16 August, the period of exposure was narrowed to the 13 days from 3 August to 15 August. Interviews with the six infected nurses outlined their timetables for this period, and identified a 13 year old boy with metastatic malignant glioma as the likely source of infection. He had been admitted to the hospital on 22 June and transferred to the paediatric intensive care unit on 10 July where he remained until his death on 7 August. Although he was never jaundiced, he was incontinent of faeces for several days before he died.

During the five days 3–7 August, the six infected nurses worked either day or evening shifts. On 4 August the junior doctor who became infected inserted a catheter into the patient. Because there was no necropsy, tissue and serum were unavailable for serological testing for hepatitis A His parents and two sisters often visited him and brought food which they shared with the patient and staff They were tested for hepatitis A (anti-HAV IgM and anti-HAV) on 15 October. At about the same time a questionnaire designed to assess risk of infection with hepatitis A was given to the 19 nurses and 10 doctors who worked in the paediatric intensive care unit during the presumed period of exposure. Staff from the adjacent paediatric unit were not included because there were no cases of hepatitis in their area.

The only secondary case, the cousin of an infected nurse, had stayed with her from 21–25 August. Although he received prophylactic gamma globulin on 7 September, signs and symptoms of clinical hepatitis, unconfirmed by antibody studies, appeared on 25 September.

## Methods

**Case definition.** The diagnosis of hepatitis A was made when appropriate clinical findings, abnormal liver function tests, and a positive IgM test for antibody to hepatitis A were present.

**Assays.** HB$_s$AG titre was determined by the AusriaTM II-125 system. Antibody to hepatitis A virus was detected by the HAVABtm procedure and IgM antibody to hepatitis A virus was identified by using the HAVABtm-M method (Abbot Laboratories).

**Questionnaire.** A questionnaire designed to assess variables associated with hepatitis A infection was sent to the 19 nurses and 10 housemen who worked in the paediatric intensive care unit and were, therefore, the most likely to have been exposed. This group included seven people (six nurses, one doctor) who became infected. The questionnaire comprised 40 questions about eating, drinking and smoking habits at work.

To analyse the results of the questionnaire and identify habits that may have been associated with an increased risk of acquiring hepatitis A, a 2 × 2 contingency table was made for each question by cross tabulating the responses to the questions and the outcome (development of hepatitis). For each table a p value was calculated by Fisher's exact test to measure the strength of an association between the question and the development of hepatitis A having arisen by chance. In addition, for each table, the odds of developing hepatitis A were computed for those who answered yes as well as for those who said no. By dividing the number of cases by the number of controls, the odds can be calculated. Results were examined for nurses alone and for nurses and doctors combined. Probabilities of $<0·05$ were accepted as significant.

## Results

**Hepatitis screening.** A total of 323 asymptomatic people who thought they had been exposed to hepatitis A underwent serological testing and received prophylactic pooled gamma globulin within 48 hours of the first case report before the extent of the outbreak was known. None of them had positive titres for $HB_sAg$, or had abnormal results of liver function tests. Demographic characteristics of the 267 employees in this group are shown in Table 1. Serological testing showed positive anti-HAV titres in 23·6% of the staff who were, therefore, immune prior to exposure.

Table 2 shows that place of birth, age, race and profession were associated with immunity. Using the method of recursive partitioning, it was found that among those people born in the United States doctors, dentists, nurses or those under the age of 40 were less likely to be immune to hepatitis A (8·8%) than native born staff who were over the age of 40 and in other professions (72·2% immune). For employees born elsewhere, being white or under the age of 30 was associated with increased risk (28·6% immune) compared with black, hispanic, and Asian members of staff who were over the age of 30 (77·1% immune).

The 56 other people who underwent serological testing and received prophylactic pooled gamma globulin were patients, or 'significant other' of exposed patients or staff. None of the 323 people who received prophylaxis with pooled gamma globulin subsequently developed clinical hepatitis A.

Serological screening of members of the family of the boy suspected of starting the outbreak 10 weeks after his death, showed that both parents were positive for anti-HAV; thus they had longstanding

Table 1 *Demographic characteristics of employees serologically tested for immunity to hepatitis*

| | *Immune (n=63)* | *No tested n=267)* | *% Immune* |
|---|---|---|---|
| Age (years) | | | |
| 15–29 | 15 | 145 | 10·3 |
| 30–39 | 20 | 78 | 25·6 |
| 40–69 | 28 | 44 | 63·6 |
| Sex | | | |
| Male | 25 | 98 | 25·5 |
| Female | 38 | 169 | 22·5 |
| Race | | | |
| White | 18 | 182 | 9·9 |
| Black, Hispanic, Asian | 42 | 82 | 51·2 |
| Mixed race | 3 | 3 | 100·0 |
| Country of birth | | | |
| USA | 30 | 212 | 14·2 |
| Europe | 2 | 6 | 33·3 |
| Latin South America | 21 | 38 | 55·3 |
| Asia | 10 | 10 | 100·0 |
| New Zealand | 0 | 1 | 0·0 |
| Job | | | |
| Dentist | 0 | 3 | 0·0 |
| Social Worker | 0 | 2 | 0·0 |
| Physiotherapist | 0 | 2 | 0·0 |
| Doctor | 4 | 47 | 8·5 |
| Paramedic | 1 | 9 | 11·1 |
| Nurse | 13 | 86 | 15·9 |
| Occupational/speech therapist | 1 | 5 | 20·0 |
| Radiologist/radiographer | 10 | 46 | 21·7 |
| Dietitian | 3 | 9 | 33·3 |
| Respiratory therapist | 5 | 14 | 35·7 |
| Security officer | 4 | 8 | 50·0 |
| Laboratory technician | 1 | 2 | 50·0 |
| Aide | 15 | 25 | 60·0 |
| Patient transporter | 5 | 5 | 100·0 |
| Other | 1 | 4 | 25·0 |

Table 2 *Results of serological tests of employees*

| *Group* | *Immune* | *Susceptible* | *% Immune* |
|---|---|---|---|
| Born in USA | | | |
| Doctor or dentist | 2 | 46 | 4·2 |
| Nurse | 7 | 69 | 9·2 |
| Other under age 40 | 8 | 61 | 11·6 |
| Other age 40 or older | 13 | 5 | 72·2 |
| Born outside USA | | | |
| White or under age 30 | 6 | 15 | 28·6 |
| Black, hispanic, Asian and age 30 or older | 27 | 8 | 77·1 |

immunity. Positive anti-HAV IgM titres in both sisters showed that their immunity was associated with recent infection.

**Questionnaire.** Results are summarised and presented for the 19 nurses alone, as this group had the greatest exposure. Because only one of 10 doctors contracted hepatitis, no conclusions about this group are possible. Examination of data from these doctors showed that the odds in favour of nurses and doctors contracting hepatitis were not significantly different.

In the group of nurses none of the p values was significant, although several of the trends were suggestive; due to the small sample size only an extreme outcome would have yielded a p value of $<0{\cdot}05$ Of the 40 questions asked, four yielded suggestive results. Table 3 shows the responses of the six patients and the 13 controls, and the odds of developing hepatitis A for both groups. Sharing food with patients or their families, drinking coffee, sharing cigarettes and eating in the nurses' office on the intensive care unit were all associated with an increased incidence of hepatitis. Furthermore, the greater the number of these four questions affirmatively answered, the more likely was the nurse to have been infected This is particularly striking when the odds of acquiring hepatitis A in nurses who answered yes to two questions are compared with those of answering yes to four questions (Table 3). In the sample of 19 nurses no pattern in the responses to the four questions was seen. Answering yes to one question, therefore, was not related to answering yes to another question.

Possible explanations for the sister of one nurse and the husband of another becoming infected may be found in the answers to the individual questionnaires by these nurses, and further interviews. The nurse whose sister caught hepatitis lived in hospital accommodation and worked the evening shift; on one occasion during the five days when infection was most likely to have occurred she returned home and prepared dinner for herself and her sister. The nurse whose husband became infected said that she borrowed and shared cigarettes, as well as taking opened packets of cigarettes home. Her husband also smoked.

Table 3 *Preference questionnaire comparing a case of hepatitis with controls in exposed susceptible nurses*

| | | | *Hepatitis* | | *Odds* |
|---|---|---|---|---|---|
| | | | *Yes* | *No* | *Yes/No* |
| A | Do you share food with patients or their families? | Yes | 4 | 4 | 1 00 |
| | | No | 2 | 9 | 22 |
| B | *Do you drink coffee from the coffee pot in the ward? | Yes | 5 | 6 | 83 |
| | | No | 1 | 6 | 17 |
| C | Do you share cigarettes? | Yes | 3 | 5 | 60 |
| | | No | 3 | 8 | 38 |
| D | Do you eat in the nurses' office in the ward? | Yes | 5 | 10 | 50 |
| | | No | 1 | 3 | 33 |
| Summary | | | | | |
| E | No of above questions (A–D) answered positively | 1 or 2 | 2 | 11* | 18 |
| | | 3 or 4 | 4 | 2 | 2 0 |

*One nurse did not respond to B but responded to A, C, and D

Table 4 *Costs for screening and prophylaxis for employees*

| *Item* | *Unit cost (US$)* | *Cost for 267 units (US$)* |
|---|---|---|
| SGPT | 7 50 | 2002 50 |
| HB$_s$AG | 11 00 | 2937 00 |
| Anti-HAV | 18 90 | 5046 30 |
| Anti-HAV-IgM | 18 90 | 5046 30 |
| Pooled gamma globulin (2 ml) | 8 42 | 2248 14 |
| Total | 64 72 | 17 279 64 |

Table 4 summarises the individual costs for each screening test used and for the pooled gamma globulin. Cost per employee and the total for all 267 employees are also shown. These are the full costs to the hospital

## Discussion

When the first six cases of hepatitis were reported, neither the source nor the magnitude of the outbreak were known; consequently, all employees, patients and their 'significant others' with potential exposure to the environment of the paediatric intensive care unit and the adjacent paediatric unit were encouraged to undergo serological testing and to receive prophylaxis. Of the 323 people who received pooled gamma globulin, 204 were asymptomatic at risk staff with normal serum SGPT activity. None of them later developed clinical hepatitis A Previous studies have shown that pooled gamma globulin given early in the incubation period can be protective in 80–90% of cases.[14 15]

During interviews with the infected nurses, it became clear that the 13 year old boy with metastatic malignant glioma, who had been incontinent of faeces for several days before he died, was probably the source of the infection. He was never jaundiced, had not had liver function tests performed during the final weeks of his illness, and necropsy was not done. There were therefore no tissue specimens or sera that could be tested for the presence of hepatitis A antigen. Furthermore, by the time of his death he had been in hospital continuously for seven weeks. Thus if he had had hepatitis he must have been infected in the hospital, and there were no other patients with hepatitis A in the hospital during this period. The staff recalled, however, that his family visited regularly and had often brought food which they shared with both staff and the boy. They also complained occasionally of not feeling well. Ten weeks after the patient's death serological testing of both his sisters showed anti-HAV IgM although they denied signs and symptoms of hepatitis. As IgM antibodies appear early and in most cases are present only for the first few months following infection,[16 17] this finding is usually regarded as specific and sensitive for recent hepatitis A.[18] Kao *et al*[19] reported that in five (13.5%) of 37 cases anti-HAV IgM persisted for longer than 200 days; towards the end of the positive period in these five patients, however, titres were very low. Without the radioimmunoassay it would have been impossible to have identified the patient as the source of infection retrospectively.

If this patient was the source, his faecal incontinence probably occurred during the prodromal phase. Viral particles have been detected in the stool of patients with hepatitis A from five to seven days before the onset of jaundice in addition to abnormal transaminase activity[20-22]; this is the time of maximum excretion of the virus for some patients. Because the diagnosis of hepatitis is not usually apparent at that stage, they may not have been appropriately isolated in the hospital. Thus the period has been reported as the most likely time for cross infection.[8-12] Some investigators have suggested that the amount of virus excreted diminishes so abruptly after the onset of jaundice and increase in transaminase activity that special isolation procedures are no longer necessary after symptoms of hepatitis.[23] Their faeces should be handled with the same precautions that would be used for all inpatients. There is, however, no universal agreement on this point. Some studies have shown that virus excretion does continue after the onset of jaundice.[24-25] Consequently, isolation is appropriate to prevent transmission of the virus.

Careful handwashing is one of the most important ways of preventing the spread of hospital acquired infection.[26] One group of investigators, however, observed the frequency of handwashing in a medical intensive care unit and found that compliance with the rule that hands should be washed after each contact with a patient was only 41%.[27] Although it was not mentioned in our questionnaire, it is likely that inadequate handwashing in the paediatric intensive care unit was an important contributing factor in the spread of the hepatitis A virus from the presumed source to the six nurses and one junior doctor.

Analysis of the data from the questionnaire given to the 19 nurses, who all had the same exposure to hepatitis A because they all cared for the boy concerned, suggested that sharing food with patients or their families, drinking coffee, sharing cigarettes and eating in the nurses' office may also have contributed to the spread of infection. These habits were more common in the six cases of hepatitis than they were in the 13 exposed but uninfected nurses. Furthermore, nurses who did three or four of these were more likely to acquire hepatitis than those who did one or two. Because eating sweets and biscuits and drinking coffee in the wards is common among hospital staff, another important prophylactic measure would be to discourage any habit that entailed touching the mouth such as eating, drinking, and smoking while on duty.

The sister and husband were primary not secondary cases because they developed hepatitis at about the same time as the nurses to whom they were related. Both nurses specifically denied ever taking food home, and neither relative ever visited the intensive care unit. Although not completely satisfactory, the most reasonable explanation seems to be some other form of faecal contamination. The nurse whose sister was infected left the intensive care unit for a short time in the middle of her shift to prepare dinner, which she shared with her sister. Probably she had not washed her hands adequately before leaving work and so contaminated their food with hepatitis virus. The nurse whose husband became ill was certain that she took cigarettes home. Because she often shared them with friends, her cigarettes may have been contaminated by her colleagues who took them from the pack without washing their hands properly after contact with patients.

Immunity to hepatitis A increases with age, is inversely proportional to social class and economic status and is found in a high proportion of the residents of underdeveloped countries where hygiene is poor.[28] Unlike hepatitis B, it is not considered to be an occupational risk for doctors. The prevalence of anti-HAV among them was similar to that among volunteers donating blood for the first time in the general population, matched for social class and economic status.[29] The rate of immunity in the 267 employees screened in this outbreak (Table 1) followed these general trends. It was highest in older people and in those who were born outside the United States of America (Table 2). Although it is independent of race,[27] the confounding variables in this sample are that non-white employees tended to be from lower socioeconomic groups who were more likely to have been born in developing countries. The 19 staff nurses and 10 paediatric house officers considered to be at greatest risk for hepatitis infection during this exposure were in the groups with the least immunity (Table 2). Data on risk and susceptibility are important for establishing priorities for immunoprophylaxis of staff following exposure to infection.

If the source of hepatitis and magnitude of the outbreak had initially been more clearly defined, fewer screening tests would have been needed In a large group of employees it may be reasonable to concentrate control measures on those at high risk of infection. The most cost effective plan, therefore, may be to give prophylaxis with pooled gamma globulin to all high risk employees and omit the screening tests.

We thank Dr Schottenfeld for reviewing this manuscript

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# Purulent pericarditis

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SUMMARY Eleven children under 16 years of age with purulent pericarditis were seen in one hospital in one year. The condition was always secondary to a septic focus elsewhere, usually staphylococcal pneumonia; its incidence after pneumonia was 0·64%, but this may be an underestimate. Clinical diagnosis can be difficult in patients with pneumonia as the heart is not always enlarged. Persistent or progressive liver enlargement was an important diagnostic feature. The presence of excess pericardial fluid was easily confirmed by echocardiography. Early diagnosis and drainage followed by continuous irrigation with 0·1% povidone iodine solution usually resulted in rapid recovery, but two patients died.

Purulent pericarditis continues to pose such diagnostic problems that most cases are diagnosed at necropsy.[1] As few necropsies are carried out in African Hospitals its real incidence is difficult to estimate. Bacterial infections, particularly pneumonia, are more common in developing than in industrialised countries, and so purulent pericarditis might be expected to be a more common disease.

Recently several workers have reported that the best treatment for purulent pericarditis is to use appropriate antibiotics and surgical drainage as soon as the diagnosis has been made.[2–7] Early aggressive treatment has reduced the mortality, which after medical treatment with antibiotics and pericardiocentesis is 43–100%.[8 9] The purpose of this study was to analyse the presentation aetiology, management, and outcome in 11 children with purulent pericarditis treated in this hospital during 1985

## Patients and methods

Eleven patients aged from 5 months to 15 years were admitted to this hospital with acute feverish illnesses complicated by purulent pericarditis. Table 1 shows the clinical presentations and Table 2 the aetiology, management, and outcome Pericardial disease was initially suspected when the fever did not resolve and cardiac tamponade developed. Persistent or progressive liver enlargement, often unresponsive to diuretics, was found to be an important sign Three patients underwent diagnostic pericardiocentesis, and five underwent echocardiography, which showed excessive pericardial fluid. One patient had both echocardiography and a diagnostic pericardial tap. Two cases presented with unequivocal evidence of acute bacterial pericarditis with tamponade so drainage was undertaken immediately without further investigations

All the children had subxiphoid pericardiostomies, seven under local anaesthesia and four under general anaesthesia with halothane or ketamine The technique is simple and common.[5–6 10 11] A piece of pericardium was sent for histological examination and a sample of pericardial fluid for culture

Irrigation was carried out in eight cases. A wide bore drain, either a three way Foley catheter or a nasogastric tube cannulated with a second catheter to allow continuous irrigation, was placed in the pericardium, connected to an underwater seal, and allowed to drain by gravity. No suction was used. The cavity was irrigated with a solution of 10 ml of 10% povidone iodine in one litre of 0·9% saline at the rate of 40 ml/h; this was continued until the effluent was clear. The drain was removed 24 hours after irrigation was stopped Postoperatively antibiotics were continued in all cases, the choice of drug depending on the bacteria cultured from the pericardial fluid

## Results

Bacteria were isolated from the pericardial fluid in eight cases, the fluid looked purulent in the remaining three but was sterile on culture. In two of these children other findings suggested tuberculosis, and in the third (case 5) the result could have been due to prolonged treatment with several antibiotics for

Table 1 *Clinical presentation of purulent pericarditis in children*

| *Case No* | *Age* | *Sex* | *Diagnosis on admission* | *Signs of pericardial disease* | | | | | *Pericardial fluid shown by* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *Fever* | *Pericardial rub* | *Hepatomegaly* | *Cardiomegaly* | *Distended neck veins* | *Pericardial tap* | *Echo-cardiogram* |
| 1 | 5 months | M | Pneumonia meningitis | + | – | + | + | + | ND | + |
| 2 | 7 months | M | Kwashiorkor, pneumonia | – | ? | + | + | ? | + | ND |
| 3 | 15 months | F | Pneumonia, heart failure | + | – | + | + | + | ND | + |
| 4 | 2 years | M | Pneumonia | – | ? | + | – | + | ND | + |
| 5 | 2½ years | F | Fever of unknown origin | + | ? | + | + | ? | ND | + |
| 6 | 2½ years | M | Pneumonia after measles | + | ? | + | + | ? | ND | + |
| 7 | 9 years | M | Pneumonia | + | ? | + | – | ? | + | ND |
| 8 | 10 years | M | Osteomyelitis | – | + | + | + | + | ND | ND |
| 9 | 11 years | M | Arthritis osteomyelitis | – | + | + | – | + | + | + |
| 10 | 12 years | M | Meningitis osteomyelitis | – | – | + | + | + | + | ND |
| 11 | 15 years | M | Pneumonia | – | – | + | + | + | ND | ND |
| Total 11 | | 2 F, 9 M | | 5 (45%) | 2 (18%) | 11 (100%) | 7 (64%) | 7 (64%) | 4 (36%) | 6 (55%) |

+=Present, –=not present, ?=not known, ND=not done

fever of unknown origin: Kawasaki disease was also suspected Table I shows the diagnosis in each case on admission; seven patients had pneumonia and three osteomyelitis. They were all febrile and were started on combinations of antibiotics for the primary illness.

The postoperative result was satisfactory in seven cases, with resolution of the clinical signs in an average of five days. One child (case 2) sustained a low grade fever until antituberculosis treatment was started, after which he improved rapidly. One patient (case 6) developed fever with enlargement of the liver two weeks after the initial pericardiostomy, and an echocardiogram showed reaccumulation of the pericardial fluid; this was drained with good effect. There were two deaths of which only one could be attributed directly to the pericarditis. One patient (case 4) died of severe bilateral pneumonia, and at necropsy there was no evidence that pericardial pus or effusion had reaccummulated. The second death (case 3) was due to delay in diagnosing the pericarditis.

## Discussion

In previous reports of purulent pericarditis in African children pneumonia and osteomyelitis were the commonest associated diseases[5 12–14] and *Staphylococcus aureus* the commonest causative organism. When pericarditis is associated with osteomyelitis diagnosis is fairly easy as it is indicated by dyspnoea and heart failure. Severe pneumonia with cardiac failure, on the other hand, may mimic cardiac tamponade, so pericarditis should always be suspected in any patient with pneumonia and heart failure. Echocardiography is useful and should be performed as soon as possible. When it is not available, however, diagnostic pericardiocentesis should be done when the clinical findings (fever, hepatomegaly, and distended neck veins) suggest that pericardial fluid has accumulated. Cardiomegaly may not always be present, and pericardial friction rub is infrequent. In our series hepatomegaly during the course of pyogenic infections was an important sign, particularly when fever failed to settle with appropriate antibiotic treatment.

In 1985, 943 out of the 3754 children under 12 years old admitted to the paediatric department of this hospital had pneumonia. Six of these also had purulent pericarditis, an incidence of 0·64% of those with pnuemonia. The true incidence is probably higher, as necropsies were not always performed in children dying from heart failure secondary to pneumonia. In 1985 mortality from pneumonia was 5·5% and no case of purulent pericarditis was diagnosed at necropsy Hospital records were available from 1979 onwards, and during 1979–84 only five cases of purulent pericarditis were recorded in children. None of these five survived, and in only one case was the diagnosis made before death. In the first six months of 1986 four new cases were diagnosed, in addition to the 11 reported here in 1985, and all four were successfully treated.

The present series of 11 cases is the largest seen in one African hospital in such a short time and may indicate that the disease is more common than is generally recognised. This fairly large number of cases is probably due to our awareness that purulent pericarditis is a complication in children with infection elsewhere and to the availability of echocardiography.

In recent years early surgical drainage has caused the mortality from purulent pericarditis to drop to between 0 and 28%.[6 10 15 16] Pericardiectomy and

Table 2 *Aetiology, management, and outcome of purulent pericarditis*

| Case No | *Results of culture of* | | *Histology* | *Antibiotic treatment* | | *Duration of irrigation (days)* | *Outcome* | *Comments* |
|---|---|---|---|---|---|---|---|---|
| | *Preoperative specimen** | *Pericardial fluid* | | *Preoperative* | *Postoperative* | | | |
| 1 | *S aureus* | *S aureus* | Non-specific inflammation | Penicillin, chloramphenicol | Cloxacillin | 2 | Good | |
| 2 | No growth | No growth | ND | Cloxacillin ampicillin | Antituberculosis drugs | 1 | Good | Cytological examination of pericardial fluid suggested tuberculosis |
| 3 | *Pneumococcus* spp | *Bacillus* spp, coliforms | Non-specific inflammation | Penicillin, kanamycin | Ampicillin, cloxacillin, gentamicin | 5 | Constrictive pericarditis, died | Nine month history of recurrent pneumonia Postoperative cardiogenic shock |
| 4 | ND | *S aureus* | Non-specific inflammation | Penicillin, kanamycin | Cloxacillin | 1 | Died | |
| 5 | No growth | No growth | Non-specific inflammation | Penicillin, ampicillin, gentamicin famicillin | Cloxacillin, gentamicin | 2 | Good | Three weeks' preoperative antibiotic treatment. ? Kawasaki's disease |
| 6 | ND | *S aureus*, non-Haemolytic streptococcus | Non-specific inflammation | Cloxacillin, kanamycin | Cloxacillin, ampicillin, chloramphenicol | 6 | Good | Redrainage two weeks after first operation |
| 7 | *S aureus* | *S aureus* | ND | Cloxacillin | Cloxacillin | ND | Good | |
| 8 | *S aureus*, *Pseudomonas* spp | *S aureus* | Non-specific inflammation | Cloxacillin, gentamicin | Cloxacillin, gentamicin | 7 | Good | |
| 9 | *S aureus* | *Bacillus* spp | ND | Cloxacillin | Cloxacillin, ampicillin | ND | Good | |
| 10 | *S aureus* | *S aureus* | ND | Penicillin, chloramphenicol | Cloxacillin, ampicillin, lincomycin | 10 | Good | |
| 11 | Coliforms | No growth | Non-specific inflammation | Chloramphenicol, gentamicin | Antituberculosis drugs | ND | Good | Mantoux test 15 mm |

*Specimens were sputum, blood, or pus from a joint pericardiostomy (pericardiotomy, pericardial window) have both been used to drain the pus; whether pericardiostomy prevents the subsequent development of constrictive pericarditis is not certain,[17] but constrictive pericarditis after pericardiectomy should be rare.[16] Reports from several workers[5 6 10] bear out our experience that early pericardiostomy with a wide bore tube to allow free drainage is effective in preventing constriction. Both techniques, however, carry a small risk of late constrictive pericarditis. None of the survivors in our series developed constriction, which usually occurs in the first postoperative year. We consider that subxiphoid pericardiostomy is preferable because it is easy and can be done quickly under local anaesthesia. If a wide bore tube is not available continuous irrigation will prevent obstruction of the tube with pus and facilitate drainage, we irrigated most of our cases despite using a wide bore tube. Driscoll *et al* reported one case in which they irrigated with povidone iodine with no adverse effects [18] We used this solution in eight of our patients with no complications attributable to it. We consider that the use of povidone iodine, coupled with the irrigation, contributed much to the rapid recovery in our patients. Irrigation is particularly important as the pus is often too thick to flow freely through the drainage tube.

We conclude that in Africa *S aureus* originating from a focus of pneumonia or osteomyelitis is a common cause of purulent pericarditis. We consider early subxiphoid pericardiostomy under local anaesthesia with continuous irrigation to be the treatment of choice in children with purulent pericarditis particularly when an anaesthetist and intensive care facilities are not available. Purulent pericarditis is more common than usually appreciated and when inadequately treated may account for an appreciable number of cases of so called idiopathic constrictive pericarditis.[12]

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# Sudden and unexpected death between 1 and 5 years

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SUMMARY Of a population of 9856 children followed up from birth, 9251 of whom underwent 24 hour tape recordings of electrocardiograms and abdominal wall breathing movements during early infancy, five died suddenly and unexpectedly at home at ages ranging from 16 months to 4 years. Postmortem examination, including full histological and microbiological investigations, failed to identify abnormalities ordinarily associated with death in all five cases. Two of the children were known to have had frequent cyanotic episodes and died during these events. In the three remaining cases there was no previous history of cyanotic or apnoeic episodes. The death of one of these three children was seen by his parents and the clinical features suggested that apnoea rather than a cardiac arrhythmia was the primary mechanism for his death.

As in infancy, sudden and unexpected death for which no adequate cause is found at necropsy seems to constitute a major component of mortality between 1 and 5 years.

In a large prospective, population based, non-intervention study into the sudden infant death syndrome (SIDS), preliminary details of which have been already reported, 9856 infants were recruited. All were tagged by the Office of Population Censuses and Surveys at the central National Health Service register so that any deaths in the study group, no matter where they occurred in the United Kingdom, would be notified. Five years later it has become apparent that five of the 15 deaths between 1 and 5 years were sudden, unexpected, and without adequate explanation at postmortem examination. An analysis of the clinical histories and modes of death in these five cases forms the substance of this report.

## Details of the population recruited and of deaths occurring up to five years later

Two population based samples of full term infants (≥37 weeks' gestation) were recruited. The first sample consisted of infants born with a birth weight of 2500 g or more in three hospitals in England between July 1980 and June 1981 (n=7496). The second sample consisted of full term infants born with a birth weight of 2500 g or less in six hospitals, including the three already mentioned between October 1979 and December 1981 (n=559). Similarly, premature infants (≤36 weeks' gestation) admitted to the special care baby units of these six hospitals during the same period were recruited (n=1801).

A small number of infants were excluded due to severe illness from birth and subsequent death before 1 month of age without an intervening period of recovery. The causes of death in this group included severe congenital anomalies, complications of extreme prematurity, and birth asphyxia.

Up to December 1986 there have been 64 deaths, 38 in the full term infants and 26 in the previously premature infants. Of these 64 deaths, 49 occurred during infancy. An adequate cause of death was recorded in 22, but 27 died suddenly, unexpectedly, and without adequate explanation at postmortem examination (cot death or SIDS). This group has been described previously.[1]

Of the children alive at the end of their first year, 15 died before their fifth birthday. An adequate cause of death was reported in 10 (Table), but in five death was sudden, unexpected, and without adequate explanation at postmortem examination. Of the postmortem examinations, three were performed by a paediatric pathologist and all five included histological and microbiological investigations.

## Case histories of sudden, unexpected, and unexplained deaths

Case 1 had no previous history of cyanotic episodes but died during an apnoeic event associated with rapidly developing cyanosis. Cases 2 and 3 had previous histories of cyanotic episodes and died during a typical episode. Cases 4 and 5 had no

Table *Causes of death between 1 and 5 years of age in a group of 9856 children*

| *Population studied* | *Explained deaths* | | *Sudden and unexpected deaths without explanation at postmortem examination* | *Total* |
|---|---|---|---|---|
| | *No* | *Cause* | | |
| Full term infants of normal birth weight (n=7496) | 3 | (1) Cardiac failure/airway obstruction varicella infection<br>(2) Hepatic failure, biliary atresia<br>(3) Accidental (drowning) | 3 | 5 |
| Full term infants of low birth weight and admitted to special care baby unit (n=559) | 1 | Bronchopneumonia, Niemann-Pick's syndrome | 2 | 3 |
| Preterm infants (n=1801) | 6 | (1) Bronchitis cerebral defect due to extreme prematurity<br>(2) Congenital heart disease<br>(3)–(5) Accidental (3) hanging, (4) road traffic accident, and (5) inhalation of smoke and multiple burns<br>(6) Bronchopneumonia cerebral defect with bulbar palsy | 0 | 6 |
| Total (n=9856) | 10 | | 5 | 15 |

previous cyanotic episodes and were found dead after they had been seen to be asleep The mode of death in cases 4 and 5 was similar to that in most sudden, unexpected, and unexplained infant deaths (cot deaths).

**Case 1.** This boy died at 4 years and was the second of three children. He was born after an uncomplicated pregnancy at 40 weeks' gestation, with a birth weight of 3280 g and an Apgar score of 9 at one minute. During pregnancy his mother did not smoke or take any medication. He was breast fed and fully immunised. Apart from minor respiratory tract illness, he was well until 4 years 4 months, when he died suddenly at home.

On the day of his death he was well and had shown no signs of a respiratory tract infection or any other illness. At about 1800h he was standing watching television when his brother pushed him and he fell lightly against the wall. He recovered posture but ran into the kitchen where his mother and father were preparing dinner. He was pointing to his chest and his mouth was wide open. He did not make any audible sounds but within 10–15 seconds of the fall became rapidly more cyanosed. At around 20–30 seconds, when he was deeply cyanosed, he fell to the floor and lost consciousness. His father had recently undergone a course of training in resuscitation but, despite mouth to mouth airway pressure, could not inflate his chest for the first minute of his unconscious state. Thereafter, his chest suddenly inflated and continued to do so with each of his father's breaths. He did not recover, however, and by the time the family doctor arrived (15 minutes later) he was pronounced dead.

The only finding at postmortem examination was lung congestion with pulmonary oedema. No foreign body was found in the airway. The upper airway and cardiovascular system were structurally normal and no micro-organisms were detected on microbiological examination.

His younger brother, aged 14 months at the time of his brother's death, had suffered two cyanotic episodes after attempts to cry in frustration. In both cases he recovered with a gasp and did not lose consciousness.

**Case 2.** This girl, who died at 18 months, was born to a single mother who was 17 at the time of birth. Her mother had smoked eight cigarettes a day during the pregnancy, which was otherwise uncomplicated. She was born at 37 weeks' gestation, with a birth weight of 2450 g and an Apgar score of 10 at one minute. She had a hare lip and cleft soft palate.

At 3 weeks she was admitted for difficulties in feeding and an upper respiratory tract infection. At 3 months her hare lip was repaired. At 9 months she suffered a lower respiratory tract infection and was treated in hospital. At 16 months she ingested half a bottle of disinfectant with no apparent ill effects.

At 17 months she presented with two cyanotic episodes, each after an attempt to cry. After each of these episodes she became drowsy and, according to her mother, was disorientated. Her family doctor found no abnormalities on clinical examination. Two further episodes occurred, the first while she was being placed into her cot and the second while in her cot and thought to be asleep. In both latter episodes her mother stimulated her and she breathed in and recovered.

She was admitted to hospital. No abnormalities were found on clinical examination and the following investigations were performed and yielded normal results: blood sugar concentration, full blood count, blood culture, lumbar puncture, and chest *x*-ray film. During this admission a cyanotic episode was observed by an experienced paediatric nurse. The child was playing, fell down, started to cry then 'held her breath', and became rapidly and severely cyanosed. The episode ended with a gasp and she fell asleep afterwards. A diagnosis of 'cyanotic breath holding' was made, the mother reassured, and the child discharged.

Two weeks later she was found cyanosed in her cot. Her mother went to wake her and found her lying still, deeply cyanosed, and sweating profusely. She was stimulated by her mother and slowly recovered consciousness. During her journey to hospital in an ambulance however, a further severe cyanotic episode occurred and she was given oxygen. This episode was accompanied by a loss of consciousness and convulsions. The morning of these episodes she had received a routine immunisation. She was admitted to hospital, largely at the request of the mother. The paediatrician explained that these were cyanotic 'breath holding' episodes and advised the mother that no treatment was necessary. At this time she remained drowsy. An eight channel electroencephalogram (EEG) was performed and showed no abnormalities. No further cyanotic episodes occurred and she was discharged home.

Five days later, while awake and being carried to bed by her mother, a further cyanotic episode occurred. Her mother ran to a nearby house with the child and the neighbour attempted mouth to mouth resuscitation. The police and ambulance men arrived and also attempted resuscitation but without success. She was pronounced dead on arrival at the hospital.

Postmortem examination showed a small child (weight<3rd centile) with a mild upper respiratory tract infection and otitis media. There was pulmonary oedema and lung congestion, but no structural abnormality of the upper airway.

**Case 3.** This girl, who died at 2 years 10 months, was the first born and only child of the mother's second marriage (the mother was 40). Her father (aged 42) had no previous children but her mother had two children from her first marriage. There was no family history of cyanotic episodes. She was born at 38 weeks' gestation, with a birth weight of 2250 g, after a pregnancy complicated by polyhydramnios and by emergency caesarean section for fetal distress during labour. The day after birth she underwent repair of a tracheo-oesophageal fistula with oesophageal atresia. She recovered well from this procedure, was breast fed, and was discharged home at 1 month.

At 3 months she began to suffer cyanotic episodes which continued thereafter with a frequency varying from three per week to one per month until her death. These episodes were witnessed by paediatricians and by nursing staff. Most were associated with eating or drinking, some occurred after an attempt to cry in association with noxious stimuli, and others occurred during sleep. For each cyanotic episode, the first event detected by the parents and hospital staff was an audible expiratory grunt. This was followed by the extremely rapid onset (within five to 10 seconds) of cyanosis. There were no apparent breathing movements, she seemed to be 'breath holding in expiration', and by 20 seconds she was deeply cyanosed and seemed unconscious. Observations by medical staff during cyanotic episodes showed no evidence of obstructed inspiratory efforts. Recovery was heralded by the sudden onset of an inspiratory breath, after which the cyanosis would decrease, although it might take up to one minute to clear completely. She would then remain hypotonic and drowsy for several hours.

Her parents never left her unattended, and she slept next to their bed. Sometimes she recovered spontaneously from a cyanotic episode without losing consciousness. For most episodes she was given mouth to mouth resuscitation or positive pressure inflation by an Ambu-bag and face mask.

In between episodes she was well apart from a loud expiratory grunt, which was most pronounced during exercise or excitement.

At 10 months she was admitted for further investigation of the cyanotic episodes. A barium swallow examination showed 'minimal and probably insignificant reflux' and the oesophagus seemed to be of normal calibre (a second barium swallow examination performed at 22 months failed to show any reflux). At bronchoscopy there seemed to be some anteroposterior narrowing of the lower third of the trachea, and cinefluoroscopy of the trachea during quiet breathing showing some evidence of narrowing during expiration. A diagnosis of tracheomalacia was considered and she was treated by aortopexy.[2] At subsequent bronchoscopy and cinefluoroscopy two weeks postoperatively the trachea seemed wider. Nevertheless, the aortopexy made no impact on the frequency or severity of the cyanotic episodes, which on two occasions occurred despite nasotracheal intubation.

During periods of unconsciousness associated with the most prolonged episodes of cyanosis, she developed convulsive movements and was sometimes incontinent of urine An EEG showed no abnormalities and treatment with anti-epileptic drugs failed to reduce or modify her cyanotic episodes. Her paediatrician considered that the convulsions were secondary to hypoxaemia and at 18 months the treatment with anti-epileptic drugs was stopped. A diagnosis of reflex anoxic seizures[3] was also considered and she was treated with atropine 150 mg three times daily. This also failed to modify the frequency or severity of cyanotic episodes.

Although developmental assessments, including one performed a week before death, yielded normal results, a minimal right sided hemiparesis was identified at 2 years. This was thought to have resulted from a particularly severe and prolonged episode of hypoxia that occurred at 18 months. At the time of this severe episode, she was resident for three days in the children's ward to cover the time after a routine immunisation.

Her fatal cyanotic episode occurred at 2 years 10 months when she was in a restaurant. She had just finished eating a sponge cake and a glass of orange squash when she looked up at her mother and stopped breathing Her facial expression indicated to her mother that she was about to have a cyanotic episode. She became rapidly cyanosed (within 10 seconds) and her mother lifted her out of the chair, carried her outside the restaurant, placed her on the pavement, and gave mouth to mouth resuscitation. She started to breathe but then stopped again. Despite the efforts of the ambulancemen she was dead on arrival at the hospital

A postmortem examination showed pulmonary oedema and a small area of oesophageal dilatation at the site of the repair of the tracheo-oesophageal fistula. The airway was structurally normal with no evidence of stenosis or malacia of the trachea or right or left main bronchus.

**Case 4.** This boy, who died at 3·5 years, was the second born of three children. His mother was 26 years old at his birth, which followed a pregnancy complicated by iron deficiency anaemia and a urinary tract infection His mother did not smoke during pregnancy He was born at 38 weeks' gestation, with a birth weight of 3060 g and an Apgar score of 8 at one minute Before death he suffered only minor illnesses typical of early childhood.

On the day of death he was put to bed at around 1830h. He shared the bedroom with his older brother, who was aged 5 years. At around 2300h his mother went, as usual, to take him to the toilet and found him dead.

At postmortem examination his weight was 14 kg (10–25th centile) and apart from patches of pulmonary oedema, there were no abnormalities that were known to be associated with sudden death. In particular, the airway was structurally normal. The pathologist recorded that the cause of death was unknown.

His older brother had suffered cyanotic episodes between 1 and 3 years of age. In one of these episodes he had lost consciousness.

**Case 5.** This boy, who died at 16 months, was the first child. His mother was aged 20 at his birth, which followed a pregnancy complicated only by maternal smoking (10 a day) and an allergic rash on the legs treated by chlorphenıramine for the last month of pregnancy. He was born at 40 weeks' gestation, with a birth weight of 2700 g and an Apgar score of 10 at one minute. Up until the time of death, he was healthy, breast fed until 14 months, and fully immunised.

The day before death the family had travelled to stay with his grandparents. He was placed in a travelling cot for his usual afternoon sleep at 1400h. The cot was in the parents' bedroom, and this was kept adequately warm by an electric heater. Three hours later his mother went to wake him and found him dead.

A postmortem examination failed to explain death. Partial atelectasis of both lower lobes of the lungs and pulmonary oedema and dilatation of the right ventricle were the only findings. The airway was structurally normal.

Shortly after the death his mother attempted suicide but was successfully resuscitated. She now has another child, who is well.

## Results of the analysis of 24 hour tape recordings on the five sudden unexplained deaths

Twenty four hour tape recordings were obtained during the first two months of life on all five cases; in case 1 at 7 and 47 days, in case 2 at 1 day, in case 3 at 16 and 52 days, in case 4 at 2 days, and in case 5 at 21 days

None of these recordings showed a cardiac arrhythmia, pre-excitation, or a prolonged QT interval. None showed prolonged apnoeic pauses. When compared with age and birth weight matched controls none showed abnormal mean heart and respiratory rates,[4 5] but case 4 showed abnormally increased levels of short apnoeic pauses and periodic breathing at 16 days.[6]

## Discussion

Sudden unexpected and unexplained deaths without adequate explanation at postmortem examination (the sudden infant death syndrome (SIDS)) constitute a major proportion of infant mortality during the first year of life. United Kingdom figures show that about 45% of all deaths during infancy and after the first week of life are categorised as SIDS.[7]

These five case reports exemplify what might be termed sudden unexplained childhood death. The five deaths occurred in the four years after infancy in a population of just under 10 000 followed up from birth. The frequency of this entity in this sample followed to the end of the fourth year of life is about 0·125 per 1000 (each year, roughly 16 times less than the incidence of SIDS (from 1·95 per 1000 live births).[7] Sudden deaths without explanation represent an important component of mortality in early childhood, as well as in infancy, accounting here for one third of the 1 to 5 year mortality.

Our original sample of infants was biased to include a higher proportion of low birthweight and preterm subjects, and therefore the prevalence of sudden unexplained child death in our population may not necessarily represent the true incidence in the United Kingdom. Nevertheless, three of the five sudden, unexplained deaths occurred in full term, normal birthweight infants.

In cases 4 and 5 the mode of death was similar to that of most SIDS victims. Apparently healthy children were found dead in bed. The tragedies were all the worse as the children were at an age when the possibility of sudden death is rarely considered by parents and when the children were established members of the family.

In case 1 there was no warning of the fatal cyanotic event. An upright posture was maintained during the first 20 seconds. As a cardiac arrhythmia would usually be accompanied by a fall in cardiac output and hypotension an apnoeic mechanism is more likely. The latter may have resulted from acute airway obstruction,[8] a seizure in the limbic area,[9] or prolonged expiratory apnoea[10–12] (cyanotic 'breath holding').[13]

In case 2 the typical history and observation of the cyanotic episodes confirmed a diagnosis of cyanotic 'breath holding'.[10–13] There was no history of stridor, ribcage retraction, or any of the other features of airway obstruction in this infant. Moreover, we could find no data that described an increased incidence of cyanotic episodes in patients with clefts in the soft palate. Prolonged expiratory apnoea has been identified as the mechanism for expiratory cyanotic breath holding episodes by Gauk[10] and from our own continued experience in 10 infants and young children.[11–12] The hallmark of this condition is the rapidity of onset and severity of the arterial hypoxaemia. Episodes are usually triggered by an experience that results in an attempt to cry. The child opens his mouth wide, makes no audible sound, and is cyanosed within five to 15 seconds. Breathing movements are ineffective in that there is no inspiratory airflow. After 20–30 seconds when cyanosis is profound, the child will lose consciousness and may start convulsing. If the child is standing at the onset of the episode he may move towards help but will eventually fall down as hypoxaemia progresses. Recovery, if spontaneous, usually occurs with a large inspiratory effort or gasp. Respiratory function tests and other investigations may be normal between apnoeic episodes. The cyanotic episodes typically consist of a short initial phase of absent respiratory efforts followed by active expiratory efforts and rapid and severe arterial hypoxaemia.[10–12] Upper airway closure also occurs,[11 12] but we emphasise that this is not the primary cause of the apnoea but an associated response: prolonged expiratory apnoeic events occur despite the bypassing of the upper airway.[11 12] As case 2 died during a typical cyanotic episode it can be concluded that the cause of her death was prolonged expiratory apnoea.

The cause of death in case 3 is less straightforward. Previous reports on the cyanotic episodes that may often follow the repair of a tracheo-oesophageal fistula have attributed the hypoxaemia to airway obstruction from tracheomalacia.[2] The extremely rapid onset of severe arterial hypoxaemia is, however, difficult to explain on the basis of tracheal obstruction and raises the possibility that, in this case, and possibly in others after tracheo-oesophageal fistula repair, prolonged expiratory apnoea may have been responsible for the cyanotic episodes. In this latter condition the rapid hypoxaemia is thought to follow apnoea at low lung volume where there is a major mismatch between ventilation and perfusion.[11 12 14] At the onset of apnoea from airway obstruction lung volume would not be expected to be below functional residual capacity and there should be enough oxygen in the lungs to delay onset of cyanosis for 30 to 40 seconds. The continuation of cyanotic episodes despite nasotracheal intubation in this child rules out *upper* airway obstruction. Other features of the cyanotic episodes in case 3 that support expiratory rather than lower airway obstructive apnoea include the lack of postmortem evidence of tracheomalacia and the expiratory rather than the inspiratory efforts noted by medical staff during cyanosis. Aortopexy also failed to reduce the frequency or severity of cyanotic episodes. In case 3 many episodes of cyanosis followed eating or drinking, raising the possibility that some of the apnoeic episodes might have been triggered by food or liquid within the oesophagus. Stimulation of oesophageal receptors has been shown to produce bronchoconstriction,[15] and in the presence of unstable alveoli this might produce a reduction in functional residual capacity, thus triggering an episode Aspiration of food into the trachea may also have triggered severe lower airway obstruction. Coughing from bronchial C fibre (irritant) receptor stimulation was not, however, a feature of the cyanotic episodes.

In a previous prospective study the incidence of cyanotic 'breath holding' episodes was reported to be 2·8%,[13] most (80%) having ceased by 6 years From these figures, 276 cases might have been expected in our sample of 9856 children, and it will be valuable to ascertain whether our ongoing follow up of this present population confirms this. Nevertheless, most have therefore not died, which perhaps explains why the condition is thought to be benign Our present findings that prolonged expiratory apnoea was almost certainly responsible for death in case 2 and possibly responsible in case 3 indicate that the condition may sometimes not be benign, a view supported by the case described by Paulson.[16] Apart from death, severe neurodevelopmental disorders may follow these episodes.[11]

In conclusion, one third of deaths in this sample of children aged 1 to 5 years were sudden and without adequate explanation at postmortem examination Prolonged expiratory apnoea was responsible for death in at least one of our five cases.

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# Compliance with gluten free diet in coeliac disease

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SUMMARY Fifty two children in whom coeliac disease was confirmed by persistent enteropathy while they were taking gluten were monitored to assess the effects of compliance with a gluten free diet (GFD). Between the ages of 17·8 and 18·5 years height (in 45 patients followed up for a mean of 14·9 years) and weight (in 43 followed up for a mean of 15·2 years) were significantly lower in those complying poorly with a GFD compared with those complying well. Of the 37 patients still attending the clinic after a mean of 25 years, having been followed up for a mean of 18·4 years, 16 who had complied well with the diet had normal or only slightly abnormal mucosal morphology whereas all 10 who had not complied had abnormal morphology. In these 10 lactase, sucrase, and alkaline phosphatase activities were significantly less than values in those who complied well. Mucosal sucrase and alkaline phosphatase activities in those who complied well were not different from those in a control population, whereas lactase activity was significantly lower. It is concluded that failure to comply with a GFD during childhood results in decreased adult stature and in persisting active enteropathy with depressed brush border enzyme activity.

Shelton reviewed 57 young adults who had been diagnosed as having coeliac disease in childhood and found that six were stunted[1]: there had, however, been a delay of at least seven years before diagnosis. Of the 57, 13 had had a clinical relapse, and 19 had low serum folate and 11 low serum iron concentrations. The initial diagnosis had been made without intestinal biopsy. Young and Pringle from a series of 110 children regarded as having coeliac disease, followed up 44 for between eight and 19 years[2]; 11 out of 20 receiving a strict gluten free diet (GFD), six out of 16 receiving a partial GFD, and only one out of eight receiving a normal diet were above the 50th height centile, and five receiving a normal diet were below the 3rd centile. No initial biopsy was done in 15 of the 110, and in the 44 followed up for some years repeat biopsies were not done, progress being assessed by anthropometric and clinical criteria.

We followed up a group of 52 children for a mean of 18·4 years to see if there was an association between their growth, general health, mucosal morphology, and enzymology and their compliance with a GFD. We believe that this is the first study in which the initial diagnosis was confirmed in all cases by the finding of persisting gluten enteropathy and in which serial biopsies were performed

## Patients and methods

We studied 52 children, 47 of whom had taken part in a previous study;[3] the mean age at diagnosis was 3·3 years (range 6 months to 12 years). The children comprised 32 girls and 20 boys, because there was no difference between the sexes in either compliance with diet or outcome the results were combined. In 42 children persisting gluten intolerance was confirmed by mucosal relapse on return to a normal diet; 10, whose dietary compliance was poor, were regarded as having persisting gluten intolerance because active mucosal enteropathy was found after a mean of five years' treatment. Intestinal biopsy samples were taken with Crosby or Watson capsules, morphological appearances being graded 0 to III[4] (0 = normal and I = slight, II = moderate, and III = severe villous aplasia); grades II and III were regarded as diagnostic of active coeliac disease. Mucosal enzymes were assayed as previously described.[5] Throughout the study the appearances on dissecting microscopy and histological examination were graded by BMcN. Specimens were assessed in batches, by dissecting microscopy some days after the biopsy and histologically some weeks later, usually without any clinical information being available. Clinical details may have been known in some instances, particularly early in the study when techniques were being developed and occasionally when there were pressing demands for a report from parents or colleagues, as we were providing a service for other patients as well as our own. Haemoglobin, serum, red cell folate, and serum iron concentrations were measured by accepted methods, some of which changed during the study. The mean number of biopsy specimens obtained in the 37 patients who attended throughout was 5·18. Height was measured during the last 15 years of the study with a Harpenden stadiometer and, before that by nursing staff with a less accurate stadiometer mounted on the wall; their technique was evaluated periodically. Height and weight were plotted on the same kind of charts throughout.[6]

Dietary compliance was assessed by BMcN or BEM, who were in clinical charge of the patients until at least their 18th year, when most were transferred to the care of CMcC. Parents and children were questioned carefully at each attendance about their diet, but detailed analysis was not attempted. We believe that in the case of preschool children compliance is usually good and it is easy for the parent to oversee the diet. With school children, however, the child's word has to be taken on trust concerning food eaten outside the house. We believe that on most occasions when a child is asked 'How often do you eat what you are not supposed to?' he gives a reasonably honest response and that our assessments of compliance were generally valid. Compliance was considered good if wheat or rye were rarely or never eaten (good GFD), moderate if the child admitted to occasional or regular indulgence in small amounts (moderate GFD), and poor if we considered that consumption of wheat products was regular and considerable or that the diet was virtually normal (poor GFD). Regular home visits by a dietitian or other health worker might have improved the accuracy of our categorisations, but we did not attempt this. Particularly in children with a poor GFD there was little if any doubt because non-compliance was readily admitted and continued despite regular exhortations from both us and the family doctors.

Table 1 *Height and weight centiles and dietary compliance in patients aged between 17·8 and 18·5 years*

| | *Good GFD (n=27)* | *Moderate GFD (n=8)* | *Poor GFD (n=10)* |
|---|---|---|---|
| Mean height centile | 53·8 | 31·2 | 26·6* |
| SEM | 6·3 | 11·0 | 8·6 |
| SD | 32·1 | 31·1 | 27·2 |
| | (n=27) | (n=7) | (n=9) |
| Mean weight centile | 60·3 | 48·5 | 32·5† |
| SEM | 5·8 | 9·5 | 11·0 |
| SD | 30·3 | 25·2 | 29·0 |

Poor *v* good GFD *p<0·02 †p<0·05

At the time of diagnosis there were no significant differences in age at diagnosis, birth weight, weight, or height between those who subsequently differed in their dietary compliance. Until the last five years of the study oatmeal was allowed in the diet, but subsequently it was discouraged.

Student's *t* test was used to analyse data; analysis was then repeated with the Wilcoxon rank sum test, and no differences between the results obtained with the two tests were found.

## Results

Height, measured between the ages of 17·8 and 18·5 years, was taken to represent final height and was recorded for 45 patients, who had been followed up for a mean of 14·9 years (range 8·25 to 17·5). Weight was available for 44, the mean period of follow up being 15·2 years (range 8·25 to 17·5) (Table 1). Mean height and weight were significantly lower in those with a poor GFD compared with those with a good GFD; measurements in those with a moderate GFD were intermediate and not significantly different. Those who complied poorly with the diet began to do so between one and four years after diagnosis. At the end of the period of review 37 patients were still attending the clinic; their mean age was 25 and they had been under observation for a mean of 18·4 years (range 8·25 to 28·5). Of the 37, 16 with a good GFD had normal or slightly abnormal mucosa (10 grade 0 and six grade I), but all 10 with a poor GFD had abnormal mucosa (three grade II and seven grade III); the 11 with a moderate GFD showed intermediate changes (seven grade I and four grade II). Lactase, sucrase, and alkaline

Table 2 *Mean lactase, sucrose, and alkaline phosphatase activity in 37 patients (mean age 25)*

| | *Control group* (n=110)* | *Good GFD (n=16)* | *Moderate GFD (n=11)* | *Poor GFD (n=10)* |
|---|---|---|---|---|
| Lactase (IU/g) | 40·2 | 26·1‡ | 17·6 | 4·6† |
| SD | 20·9 | 12·1 | 15·9 | 2·7 |
| SEM | 2·0 | 3·0 | 4·8 | 0·9 |
| Sucrase (IU/g) | 60·3 | 53·0 | 44·0 | 17·6† |
| SD | 26·2 | 18·8 | 26·8 | 10·2 |
| SEM | 2·5 | 4·7 | 8·5 | 3·1 |
| Alkaline phosphatase (IU/mg) | 18·2 | 17·7 | 15·5 | 5·5† |
| SD | 5·6 | 5·2 | 9·5 | 2·9 |
| SEM | 0·5 | 1·3 | 3·0 | 0·9 |

†Poor *v* good GFD, p<0·001 ‡good GFD *v* controls p<0·001
*Controls were matched for age.[5]

phosphatase activities were all significantly lower in the 10 with a poor GFD compared with the 16 with a good GFD those with a moderate GFD again occupying an intermediate position (Table 2). Sucrase and alkaline phosphatase activities in those having a good GFD were not significantly different from those in controls, but lactase activity remained significantly less. In these 37 patients there were no significant differences in haemoglobin, serum iron, or red cell folate concentrations between the three dietary groups.

## Discussion

Failure to adhere to a GFD retards growth and results in decreased adult stature It also results in persisting active enteropathy in the upper intestine with decreased activity of those brush border enzymes that were assayed. We believe that patients with such active enteropathy will sooner or later suffer from further effects of chronic malabsorption, particularly mineral and vitamin deficiencies, and there may be possible adverse effects on fertility in women

It is disappointing that compliance in adhering to a GFD was poor in so many cases and that as many as 15 out of 52 patients eventually stopped attending the clinic. In this part of the country coeliac disease has been given a lot of publicity in the media and there is an active branch of the Irish Coeliac Society, so we presume that dietary non-compliance is due to the natural rebellion of teenagers and young adults against a restriction on their behaviour whose basis they will not accept. The most important question in the long term is whether adherence to a GFD will reduce or minimise the risk of early death and gut malignancy, or both. Among 547 patients with coeliac disease attending this centre 44 have died at a mean age of 56·3 years 23 of them from malignant disease of the gut at a mean age of 57·5 years. There is no evidence so far about whether a GFD reduces these risks, but it has been our policy to inform children who are reaching a responsible age about them Even though we cannot definitely assure them that keeping to a GFD will ensure a normal life span, we can be certain about the adverse effects of non-compliance on growth and almost certain about effects on future health.

The failure of lactase activity to return to normal in patients receiving a good GFD is something we have previously reported[7] and has also been found by other groups. Possibly lactase is more readily suppressed by gliadin than sucrase and alkaline phosphatase, and its failure to return to normal activity may be due to small amounts of gliadin in a 'good' GFD. One study proposed that a strict GFD did lead to normal lactase activity because the measurements, though lower than in controls, were not significantly so.[8] There is also some evidence that lactase activity in first degree relatives of patients with coeliac disease is lower than that in a control population.[9]

Since the paper was submitted, four of the 15 who had stopped attending returned for review. All said that they were keeping to strict gluten free diets. At a mean age of 27·5 years, having been followed up for a mean of 22·7 years, their mean height centile was 74. Biopsies have not yet been done.

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# Ethnic differences in incidence of very low birthweight and neonatal deaths among normally formed infants

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SUMMARY The incidence of very low birthweight babies (less than 1500 g) and neonatal mortalities in this group were analysed for the 15 608 births to mothers of various racial origins at this hospital during the years 1979–82 inclusive. Very low birth weight occurred less commonly in the European (9·1/1000) and Pakistani (10·1/1000) groups and most commonly in the West Indian group (23·2/1000). Neonatal survival in West Indians, however, was better than in any other group. Analysis of the stillbirths weighing less than 1500 g showed a lower rate in the West Indians compared with that of the European, Pakistani, and Indian groups. There was no evidence of a higher incidence of 'light for dates' in very low birthweight West Indian neonates.

Perinatal survival varies nationally and internationally. Improved neonatal care services have contributed to the declining perinatal mortality in Britain.[1] This has resulted in an increased survival of very low birthweight infants and has prompted a more careful examination of the relevant factors.[2] One factor, which has been studied in the United States of America, but which has received little attention in Britain, is the effect of the ethnic group of the mother. Comparing low birthweight blacks and whites in the United States, the survival was higher in the black population.[3 4] In this country neonatal mortality in Asians and non-Asians was examined and preterm delivery not found to be a problem in Asians, most deaths being due to lethal congenital malformation.[5]

The aim of this study was to examine the incidence of very low birthweight babies and the neonatal deaths (first 28 days) delivered at this hospital of normally formed infants born to Indian, Pakistani, West Indian, and European mothers in the area of the West Birmingham Health Authority. Particular attention was paid to possible differences between the survival of West Indian and European very low birthweight babies.

## Patients and methods

The records of all booked and unbooked deliveries at this hospital between 1979–82 inclusive were examined. Of the 15 608 babies born during this time, 706 were excluded because the mother was not from Indian, Pakistani, West Indian, or European ethnic groups. Bangladeshi mothers accounted for 475 of the 706 exclusions, but the numbers were too small to justify a detailed analysis. A further 151 births with major lethal and non-lethal congenital abnormalities were excluded but are described elsewhere.[6] The incidence of very low birthweight (defined as infants weighing less than 1500 g) was calculated, together with the normally formed stillbirth and neonatal mortality in the total population and the very low birthweight groups.

The correlation between neonatal survival and birthweight was modelled to fit a sigmoid curve (a logistic regression analysis using maximum likelihood) Ordinary regression analysis would have been inappropriate as it does not deal adequately with the definitive nature of survival or mortality. The best clinical estimate of gestation was available for 299 of the 435 infants weighing less than 2000 g, and the mean birth weight for gestation groups (in weeks) up to and including 33 weeks was calculated.

## Results

The neonatal mortality per thousand of normally formed infants over the four years was 6·2 for the total population. It was lowest in the European

Table 1 *Births and deaths (Rate per 1000)*

| | *Indian* | *Pakistani* | *West Indian* | *European* |
|---|---|---|---|---|
| Total births | 4185 | 2193 | 1859 | 6514 |
| Stillbirths | 31 (7·4) | 20 (9·1) | 9 (4·8) | 42 (6·4) |
| Livebirths | 4154 | 2173 | 1850 | 6472 |
| Neonatal deaths | 26 (5·3) | 17 (7·8) | 14 (7·6) | 31 (4·8) |
| Early neonatal deaths | 26 (5·3) | 16 (7·4) | 14 (7·6) | 21 (3·2) |
| Late neonatal deaths | 0 | 1 (0·4) | 0 | 10 (1·5) |
| Births <1500 g | 68 | 26 | 46 | 72 |
| Stillbirths | 14 (206) | 4 (154) | 3 (65) | 13 (181) |
| Livebirths | 54 (13·0)** | 22 (10·1)** | 43 (23·2)$^{+++}$ | 59 (9·1)*** |
| Neonatal deaths | 22 (407) | 12 (545) | 12 (279) | 25 (424) |
| Early neonatal deaths | 22 (407) | 11 (500) | 12 (279) | 19 (322) |
| Late neonatal deaths | 0 | 1 (45) | 0 | 6 (102) |
| Births 1000–1499 g | 44 | 15 | 31 | 55 |
| Stillbirths | 12 | 2 | 1 | 11 |
| Livebirths | 32 (7·7)* | 13 (6·0)*** | 30 (16·2)$^{+++}$ | 44 (6·8)*** |
| Neonatal deaths | 5 (156) | 4 (308) | 2 (67) | 11 (250) |
| Early neonatal deaths | 5 (156) | 3 (231) | 2 (67) | 7 (159) |
| Late neonatal deaths | 0 | 1 (77) | 0 | 4 (91) |
| Births <1000 g | 24 | 11 | 15 | 17 |
| Stillbirths | 2 | 2 | 2 | 2 |
| Livebirths | 22 (5·3)$^{+}$ | 9 (4·1) | 13 (7·0)$^{++}$ | 15 (2·3)** |
| Neonatal deaths | 17 (773) | 8 (889) | 10 (769) | 14 (933) |
| Early neonatal deaths | 17 (773) | 8 (889) | 10 (769) | 12 (800) |
| Late neonatal deaths | 0 | 0 | 0 | 2 (133) |

Difference from the West Indian group *$p<0·05$ **$p<0·01$, ***$p<0·001$, difference from the European group $^{+}p<0·05$, $^{++}p<0·01$, $^{+++}p<0·001$, statistical analyses using $\chi^2$ with Yates' correction.

population at 4·8 but higher in the other ethnic groups (Indian 6·3; Pakistani 7·8; and West Indian 7·6, Table 1).

Of the four ethnic groups, the lowest incidence of very low birthweight occurred in the European and Pakistani groups at 9·1/1000 and 10·1/1000, respectively, and the highest incidence in the West Indian group at 23·2/1000 (Table 1). This pattern was repeated in both the very low birthweight subdivisions—that is, less than 1000 g and 1000–1499 g inclusive (Table 1).

The very low birthweight specific neonatal mortalities were highest in the Europeans and Pakistanis at 424/1000 and 545/1000, respectively, and lowest in the West Indians at 279/1000 (Table 1). There was no suggestion that low birthweight West Indian perinatal losses occurred as stillbirths (Table 1).

The logistic regression analysis for the probability of survival against birthweight seemed to show the improved survival of West Indians, compared with that of other ethnic groups at all birthweights, in the very low birthweight range (Table 2). The Indian babies survived better than their Pakistani and European counterparts. The probability of survival of neonates weighing 1000 g may be taken as an example when a value of 0·75 was obtained for West Indians, 0·52 for Indians, 0·39 for Europeans, and 0·32 for Pakistanis.

There was no evidence of a higher incidence of light-for-dates or growth retarded neonates in the West Indian group (Table 3).

Table 2 *The probability of neonatal survival against birthweight (in 100 g increments) for each ethnic group*

| *Birthweight g* | *Probability* | | | |
|---|---|---|---|---|
| | *Indian* | *Pakistani* | *West Indian* | *European* |
| 500 | 0·06 | 0·04 | 0·10 | 0·04 |
| 600 | 0·11 | 0·07 | 0·18 | 0·07 |
| 700 | 0·17 | 0·10 | 0·30 | 0·11 |
| 800 | 0·26 | 0·18 | 0·45 | 0·18 |
| 900 | 0·38 | 0·23 | 0·61 | 0·27 |
| 1000 | 0·52 | 0·32 | 0·75 | 0·39 |
| 1100 | 0·65 | 0·43 | 0·85 | 0·52 |
| 1200 | 0·76 | 0·54 | 0·92 | 0·64 |
| 1300 | 0·85 | 0·65 | 0·95 | 0·75 |
| 1400 | 0·91 | 0·75 | 0·98 | 0·84 |
| 1500 | 0·94 | 0·83 | 0·99 | 0·90 |
| Total No | 139 | 49 | 87 | 160 |

Derived using a logistic regression analysis the upper limit of the sample was 2000 g.

Table 3 *Mean birthweight (g) for gestation up to 33 weeks (Stillbirths have been excluded)*

| *Gestation (weeks)* | *Indian* | *Pakistani* | *West Indian* | *European* |
|---|---|---|---|---|
| 24 | 590 | 660 | | 560 |
| 25 | 855 | | | 690 |
| 26 | 753 | 827 | 907 | 1053 |
| 27 | 983 | 1013 | 1020 | 863 |
| 28 | 1010 | 1170 | 1087 | 1115 |
| 29 | 1280 | | 1144 | 1365 |
| 30 | 1291 | 1360 | 1253 | 1468 |
| 31 | 1538 | 1355 | 1470 | 1371 |
| 32 | 1481 | | 1693 | 1735 |
| 33 | 1827 | 1990 | 1823 | 1733 |

## Discussion

This study has shown a higher incidence of very low birthweight neonates in the West Indian population compared with several other ethnic groups. This finding does not seem to be due to a higher incidence of light-for-dates neonates in the West Indian group, and although gestation has not been documented as accurately as birth weight, the conclusion must be that more West Indian neonates are delivered at the shorter gestations. Without knowing the cause of preterm labour in many cases, any further conclusions must be speculative, but ethnic variation in the distribution of gestation must represent one explanation.

Survival of the very low birthweight West Indian babies was better than in any other ethnic group. If this is mainly or entirely due to ethnic considerations the finding might agree with the comparison made between blacks and whites in the United States, as might be expected, as the Dudley Road Hospital West Indian population is of similar extraction to the American black population Caution is needed, however. the numbers are small. Although it was not possible to confirm the improved survival of small West Indian babies, these findings are consistant with those of other reports,[3 4] and the consistency of a trend over several studies, particularly those undertaken in different places, is more convincing than statistical significance in any one study. The fact that the stillbirth rate for West Indians in the very low birthweight group was low excluded the possibility of more small West Indian fetuses dying before or during labour, and therefore made the figures for the neonatal mortalities smaller.

The traditional method of analysing neonatal survival is in terms of birthweight groups. This method, although also used here, has three disadvantages. The first is that there is not agreement about limits: those used in *British Births 1970*[7] differ from those used in the *Scottish Perinatal Mortality Survey 1977–1981*.[8] The second disadvantage is that the birthweight groups are large enough for there to be a significant difference between survival at the top and bottom of the range. The third disadvantage is digit preference combined with the artificially imposed limits of the birthweight groups, especially around the important 1000 g value. This study used a binomial logistic regression analysis to examine the correlation between neonatal survival and birth weight This is a technique that is ideally suited to, but has not been widely used in, the field of perinatal audit. Although it would have been desirable to attempt to separate the effects of birth weight and gestation by a multivariate analysis, the correlation between the two is so high that the multivariate would be unlikely to yield trustworthy results.

Finally, it must be emphasised that the ethnic group of the mother was the only factor examined in this study. Other confounding variables, such as social class, maternal age, and ultimate family size, are known to influence both preterm labour and perinatal mortality. A detailed examination of such factors, however, would require a much larger study

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# Severe pre-eclampsia and infants of very low birth weight

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SUMMARY The effect of severe pre-eclampsia on the outcome of infants of very low birth weight was studied in a prospective case control study of 35 pairs of infants of comparable gestation. Significantly more infants were delivered before the onset of labour and by caesarean section in the group with pre-eclampsia. These babies tended to be smaller and had a higher incidence of hyaline membrane disease, patent ductus arteriosus, pulmonary air leak, and hypotension. They also required more intensive treatment with oxygen and mechanical ventilation. The significant difference in birth weight was still apparent at 2 years of age. Although the mean psychomotor developmental index and the incidence of specific neurodevelopmental impairments were not significantly different between the two groups, survivors in the group born to pre-eclamptic mothers had a significantly lower mean mental developmental index, and significantly more of these children had one or more impairments compared with the control group at 2 years of age.

Pre-eclampsia occurring in the second trimester or early in the third trimester differs from late onset disease not only in its serious maternal morbidity but in its high perinatal mortality and morbidity.[1 2] In severe pre-eclampsia neonatal outcome has been reported to be influenced by both the disease and the administration of antihypertensive and anticonvulsant drugs to the mother.[3] The aim of this study was to determine the effects of severe pre-eclampsia and its treatment on the neonatal course and long term outcome of very low birthweight (VLBW, <1500 g) infants.

## Patients and methods

At this centre a perinatal database is established prospectively from admission for all VLBW infants. In the four years before this study 71 (17%) of 413 VLBW infants were born to mothers with severe pre-eclampsia. In this birthweight group comparison of the infants born to mothers with and without pre-eclampsia showed a significant difference in gestational age because significantly more infants in the pre-eclamptic group were small for gestational age. We therefore undertook a prospective case control study to define more clearly the effects of severe pre-eclampsia. Thirty five VLBW infants born to mothers with severe pre-eclampsia from 1982 to 1984 were compared with 35 infants born at about the same time to normotensive mothers and matched for gestation, sex, and survival. All the VLBW survivors had clinical, neurological, and psychological assessments at 2 years of age corrected for prematurity.

Severe maternal pre-eclampsia was diagnosed when the mother had a resting blood pressure of over 140/90 mm Hg, persistent proteinuria without urinary tract infection, and generalised oedema before 32 weeks of gestation. Babies were considered small for gestational age when the birth weight was below the 10th centile based on intrauterine growth charts derived from a Melbourne population.[4] Hyaline membrane disease was diagnosed when all the following criteria were present: respiratory distress not attributable to other causes; retraction and poor air entry during spontaneous respiratory efforts, chest *x*-ray films showing diffuse fine granular infiltrates persisting at least until the third day; fractional inspired oxygen ($FiO_2$) greater than 0·3 to maintain an arterial oxygen tension of over 8·0 kPa beginning during the first 12 hours and lasting at least three days; and a maximum $FiO_2$ requirement greater than 0·4. Patent ductus arteriosus was diagnosed if there was a precordial systolic or continuous murmur or echocardiographic evidence of a left to right shunt or both. Neurological impairment at follow up was defined as cerebral palsy of any type or severity, developmental delay with a mental developmental index more than two standard deviations below the mean on the Bayley scales of infant development, blindness, or sensorineural deafness.

Statistical analysis was by the $\chi^2$, Fisher's exact, and paired $t$ tests as appropriate.

## Results

Table 1 shows the significant differences in maternal and obstetric factors between the 35 infants born to mothers with severe pre-eclampsia and the 35 matched controls. Though none of the mothers in the control group had complications associated with pre-eclampsia such as generalised oedema, disseminated intravascular coagulation, renal failure, neurological symptoms, or liver dysfunction, significantly more had chorioamnionitis and antepartum haemorrhage. Significantly more infants of mothers with severe pre-eclampsia were delivered before the onset of labour and by caesarean section. Caesarean section was carried out for maternal indications in 25 cases and for fetal distress in seven. The range of drugs given to the mothers before delivery was appreciably different in the two groups. The mothers with pre-eclampsia were given methyldopa (17 mothers), magnesium (14), hydralazine (10), chlormethiazole (nine), β blockers (eight), anticonvulsants (six), diazepam (five), and diuretics (three). The control mothers did not receive these drugs Salbutamol was used in nine control mothers in an effort to stop their preterm labour but was not given to those with pre-eclampsia. Betamethasone was given to one mother with pre-eclampsia and two in the control group.

The infants in the two groups were appropriately matched for gestational age (mean 28·9 (SD 2·0) weeks *v* 28·2 (2·0) weeks), male to female ratio (15:20 *v* 17:18) and two year survival (77% *v* 80%). Table 2 shows the significant differences in neonatal

Table 1 *Significant differences in maternal and obstetric variables*

| | *Pre-eclampsia group (n = 35)* | *Control group (n = 35)* | *P* |
|---|---|---|---|
| Mean (SD) maximum blood pressure (mm Hg) | | | |
| Systolic | 178 (28) | 126 (13) | <0·00025 |
| Diastolic | 114 (12) | 77 (8) | <0·00025 |
| No (%) with | | | |
| Proteinuria | 35 (100) | 1 (3) | <0·00025 |
| Oedema | 35 (100) | 0 | <0·00025 |
| Disseminated intravascular coagulation | 6 (17) | 0 | <0·02 |
| Renal failure | 5 (14) | 0 | <0·02 |
| Neurological deficit | 5 (14) | 0 | <0·02 |
| Liver dysfunction | 3 (9) | 0 | <0·05 |
| Fever | 0 | 7 (20) | <0·0125 |
| Membranes ruptured >24 h | 0 | 9 (26) | <0·0125 |
| Antepartum haemorrhage | 1 (3) | 10 (29) | <0·0125 |
| Presence of labour | 5 (14) | 31 (89) | <0·0125 |
| Caesarean section | 32 (91) | 10 (29) | <0·00025 |

Table 2 *Significant differences in neonatal factors*

| | *Pre-eclampsia group (n = 35)* | *Control group (n = 35)* | *P* |
|---|---|---|---|
| Mean (SD) birth weight (g) | 920 (187) | 1067 (159) | <0·0005 |
| Mean (SD) birth weight centile | 28 (22) | 49 (23) | <0·0005 |
| Mean (SD) birth length centile | 26 (25) | 43 (23) | <0·0005 |
| Data on admission (means (SD)) | | | |
| Packed cell volume | 0·51 (0·08) | 0·46 (0·09) | <0·02 |
| White cell count ($\times 10^9$/l) | 16·8 (11·9) | 19·1 (9·4) | <0·0125 |
| Platelet count ($\times 10^9$/l) | 132 (53) | 246 (89) | <0·02 |
| Systolic blood pressure (mm Hg) | 41 (13) | 45 (14) | <0·05 |
| Neonatal events | | | |
| No (%) with white cell count $<6\times 10^9$/l | 12 (34) | 3 (9) | <0·0125 |
| No (%) with platelets $<150\times 10^9$/l | 14 (40) | 5 (14) | <0·0125 |
| Mean (SD) volume expansion, day 1 (ml) | 17 (16) | 14 (15) | <0·05 |
| No (%) with hypotonia | 9 (26) | 2 (6) | <0·05 |
| No (%) with feed intolerance | 5 (14) | 0 | <0·05 |
| Mean (SD) age meconium passed (days) | 4·9 (6·8) | 2·6 (2·3) | <0·0005 |
| No (%) with hyaline membrane disease | 29 (83) | 15 (43) | <0·0005 |
| No (%) with patent ductus arteriosus | 22 (63) | 11 (31) | <0·05 |
| No (%) with pulmonary air leak | 14 (40) | 7 (20) | <0·05 |
| Mean (SD) length of hospital stay (days) | 65 (85) | 40 (51) | <0·05 |
| Respiratory treatment | | | |
| Mean (SD) duration of oxygen treatment (days) | 48 (77) | 21 (31) | <0·02 |
| Mean (SD) maximum $FiO_2$ | 0·70 (0·28) | 0·57 (0·32) | <0·02 |
| No (%) given mechanical ventilation | 30 (86) | 23 (66) | <0·05 |
| Mean (SD) duration of ventilation (days) | 30 (34) | 17 (26) | <0·02 |
| Mean (SD) maximum peak pressure (kPa) | 2·55 (1·37) | 1·67 (1·47) | <0·05 |
| Mean (SD) maximum rate (beats/min) | 47 (15) | 37 (11) | <0·0025 |

characteristics and problems. Infants of mothers with severe pre-eclampsia fell within lower birthweight and length centiles This intrauterine growth retardation was associated with a higher packed cell volume at birth. Other haematological abnormalities included leucopenia and thrombocytopenia (no infants in the pre-eclampsia group had septic complications). The systolic blood pressure on admission was lower in the pre-eclampsia group, who also required a higher volume of blood or colloid in the 24 hours after birth to maintain normal blood pressure. In the first week after birth hypotonia feed intolerance with abdominal distension and delay in passage of meconium were also more common in this group.

Cardiorespiratory disorders of hyaline membrane disease, patent ductus arteriosus, and pulmonary air leak were more common in the pre-eclampsia group, as was use of mechanical ventilation (Table 2). In this group 29 (97%) of 30 ventilated infants had hyaline membrane disease, compared with 15 (65%) of 23 infants in the control group. They required longer and more intensive oxygen treatment and mechanical ventilation and spent longer in hospital than the control group. When only those infants ventilated for hyaline membrane disease were compared the pre-eclampsia group had similar requirements for oxygen support ($FiO_2$ 0·80 (0·20) *v* 0·8[illegible] (0·25)) but needed significantly longer periods of treatment with oxygen (50 (84) days *v* 28 (31) days, $p<0·05$) and mechanical ventilation (36 (35) days *v* 24 (30) days, $p<0·05$), greater maximum peak pressure (3·04 (0·931) kPa *v* 2·65 (0·981) kPa, $p<0·05$), and greater maximum ventilator rate (50 (14) beats/min *v* 40 (12) beats/min, $p<0·05$).

There were no significant differences between the two groups in head circumference centile at birth; Apgar scores at one and five minutes; admission temperature, arterial blood pressure, pH, and ratio of arterial oxygen tension to $FiO_2$; persistent pulmonary hypertension and haemorrhagic pulmonary oedema; periventricular haemorrhage, leucomalacia and posthaemorrhagic hydrocephalus; seizures and hypocalcaemia, hyperbilirubinaemia; necrotising enterocolitis, renal failure; and retinopathy of prematurity

At the two year assessment no significant differences in centiles of height and head circumference were found, but weight centiles remained significantly lower in the pre-eclampsia group (Table 3) The mean psychomotor developmental index on the Bayley scales of infant development was similar in the two groups. Survivors in the pre-eclampsia group, however, had a significantly lower mean mental developmental index. Furthermore, six (22%) of 27 survivors in this group compared with one (4%) of 26 survivors in the control group had one or more impairments ($p<0·05$). The incidence of specific impairments, however, was not significantly different between the groups Of the six impaired survivors in the pre-eclampsia group, four had hemiplegia secondary to neonatal intraventricular haemorrhage or intracerebral haemorrhage or both, one had severe developmental delay due to periventricular haemorrhage in utero, and one had spastic diplegia and sensorineural deafness associated with normal findings on cerebral ultrasonography. Four of these six impaired survivors were small for gestational age at birth. The single impaired survivor in the control group was not small for gestational age at birth but had spastic quadriplegia and severe developmental delay due to meningitis. At two years the growth of the survivors who had impairment was no different from that of those who were neurodevelopmentally normal

Table 3 *Comparison of outcome in survivors. Data expressed as mean (SD) and number (per cent)*

| | *Pre-eclampsia group (n = 27)* | *Control group (n = 26)* |
|---|---|---|
| Growth centiles | | |
| Mean (SD) weight | 16 (19) | 28 (30)* |
| Mean (SD) height | 17 (20) | 27 (27) |
| Mean (SD) head circumference | 42 (21) | 46 (31) |
| Bayley scores | | |
| Mean (SD) mental developmental index | 94 (25) | 106 (21)* |
| Mean (SD) psychomotor developmental index | 89 (22) | 93 (15) |
| No (%) of survivors with one or more impairments | 6 (22) | 1 (4)* |
| Type of impairment | | |
| No (%) with cerebral palsy | 4 (15) | 1 (4) |
| No (%) with developmental delay | 3 (11) | 1 (4) |
| No (%) with blindness | 1 (4) | 0 (0) |
| No (%) with sensorineural deafness | 1 (4) | 1 (4) |

*$p<0·05$

## Discussion

Three case control studies have previously been reported, each concerning 22 to 29 infants born to mothers with severe pre-eclampsia.[1-3] Two of these studies were carried out in groups with a mean gestation of 32 weeks[1 3] compared with a mean of 29 weeks for the 35 infants in our study The remaining study reported on 29 infants with a mean gestation of 28 weeks,[2] but because pregnancies complicated by severe pre-eclampsia were treated conservatively the neonatal survival rate was only 28% (eight survivors) compared with the two year survival rate of 77% in the present study. Severe early pre-eclampsia is usually associated with progressive deterioration in both mother and baby. When it is managed conservatively the unfavourable intrauterine conditions cause all the stillbirths and most of the neonatal deaths.[1-3]

The incidence of small for gestational age infants reported in mothers with severe pre-eclampsia has ranged from 20% to 80%.[1-6] Cumulative data from these studies showed that 226 (28%) of 817 infants reported on were small for gestational age. This compares with 15 (43%) of 35 infants in the present study.

The aetiology of pre-eclampsia is unknown. Abnormalities noted in the mothers in this study showed clinically that the disease affects several systems. Severe vasoconstriction probably leads to ischaemic changes in various organs, endothelial damage, and deposition of platelets and fibrin thrombi. This vasoconstriction may result from the presence of a circulating vasoconstricting substance or the absence of a normally present vasodilator.[8 9] Because this effect on vascular tone is found in fetal plasma at birth[9] the incidence of patent ductus arteriosus in the pre-eclampsia group may be related to the maternal disease. Neonatal thrombocytopenia and leucopenia have been reported in pre-eclampsia.[10 11] A highly significant correlation between maternal and neonatal platelet counts strongly supports a common pathological process [3] Neonatal hypotonia, feed intolerance, and delayed passage of meconium have also been reported in infants of mothers with severe pre-eclampsia.[3] These problems were thought to be associated with treatment of the mother with magnesium sulphate,[12 13] which was used in 40% of our mothers with pre-eclampsia. Furthermore, the mothers of five of the nine hypotonic infants were treated with intravenous diazepam just before delivery The increased incidence of hypotension in the pre-eclampsia group may well reflect the variety of antihypertensive drugs given to the mothers.[14]

The severity of uteroplacental insufficiency affecting the fetus in severe maternal pre-eclampsia was reflected in the rate of intrauterine growth retardation (43%) and the high packed cell volume at birth in our study Two previous studies reported significantly lower Apgar scores at one and five minutes in infants born to mothers with pre-eclampsia compared with control infants, and this was attributed to severe uteroplacental insufficiency.[3 7] No difference in Apgar scores was found in the present study, in which the caesarean rate was 91% (32/35) in mothers with severe pre-eclampsia. The arterial pH on admission was also similar in the pre-eclampsia and control groups, suggesting that timely delivery of the compromised fetuses could have prevented the development of severe birth asphyxia.

The present study showed that VLBW infants born to mothers with severe pre-eclampsia of early onset had a significantly higher incidence of hyaline membrane disease than the control infants. They also had a significantly higher incidence of associated cardiorespiratory disorders, such as patent ductus arteriosus and pulmonary air leak, and significantly higher requirements for and a longer duration of treatment with oxygen and mechanical ventilation. One previous study reported an identical incidence of severe respiratory disease,[3] and another reported a higher incidence of hyaline membrane disease[7] in the pre-eclampsia group compared with the control group, though the difference did not reach significance. It has also been reported that the incidence of hyaline membrane disease, including both mild and severe forms, was significantly lower in preterm infants born after pregnancies complicated by pre-eclampsia compared with those born after uncomplicated pregnancies.[15] The incidence of severe disease in that study, however, which used a similar definition of hyaline membrane disease to that in our study, did not differ significantly between the two groups; the incidence of severe disease was higher in the pre-eclampsia group after caesarean section compared with the uncomplicated group. One difference between that study[15] and the present one was in the incidence of caesarean section in the pre-eclampsia group (33% compared with 91% in the present study); most sections were performed before the onset of labour. It has been shown that, compared with preterm infants born vaginally, those born by caesarean section, particularly before the onset of labour, have a much greater risk of severe hyaline membrane disease [16] That labour has a beneficial effect on neonatal lung function is beyond doubt.[17] It seems to have a central role both in initiating the absorption of fetal lung liquid and in promoting surfactant secretion, though how these effects are mediated remains uncertain. A recent study showed that preterm infants born by caesarean section to mothers with pre-eclampsia of early onset had a higher, though not significantly different, incidence of hyaline membrane disease than control infants, and no evidence was found of a raised fetal serum cortisol concentration, which had been implicated in the induction of fetal pulmonary maturation in pregnancies complicated by pre-eclampsia [18]

The fetal growth rate of infants born after pregnancies complicated by severe pre-eclampsia was affected by adverse maternal and placental factors. Once released from the intrauterine environment, infants whose growth deviates from the norm at birth show a strong tendency to revert towards the mean.[19] By 2 years of age growth in height and head circumference was normal but weight was not in the pre-eclampsia group. We previously reported that the early growth rate in extremely preterm infants small for gestational age was higher than that in those who were the appropriate weight for gestation,[20] and others have shown that growth catches up by the age of 3 years [21]

Maternal hypertension is associated with a significant developmental delay in gross motor, fine motor, and visual motor functions in early childhood.[22] Epidemiological studies have also shown that the incidences of pre-eclampsia and intrauterine growth retardation are significantly increased in children with cerebral palsy compared with the normal population.[23] Although our case control study did not show a difference in the psychomotor developmental index or incidence of specific impairments between the two groups, the mental developmental index was significantly lower and more children had one or more impairments in the pre-eclampsia group. Four of the six impaired survivors in this group had neonatal periventricular haemorrhages to explain their impairments, but the origin of the impairment in the remaining two survivors was antepartum.

The timing of delivery in women who develop severe pre-eclampsia during the second trimester is difficult. The potential benefit of increased fetal maturity from delaying delivery must be balanced against the risk of fetal hypoxia and sudden intrauterine death or severe growth restriction, which includes retardation of head growth.[7] Progressive deterioration in maternal wellbeing may also expose the mother to severe morbidity or even death. As a result the obstetrician is often forced to deliver the infant despite fetal immaturity. Our observations indicate that VLBW infants born to mothers with severe pre-eclampsia have significantly more neonatal morbidity than those of a similar gestational age born to normotensive mothers. It is, therefore, important to anticipate and manage these neonatal problems appropriately, as they compound those of very preterm birth, for which these infants are already at risk.

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# Epidemiology of facial clefts

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SUMMARY Data from the Glasgow Register of Congenital Malformations were used to investigate the epidemiology of congenital facial clefts over the period 1974–85. Facial clefts were registered in 247 infants representing a prevalence of 1·56 per 1000 total births. Cleft palate was more common than cleft lip, with cleft lip and palate occupying an intermediate position. More than half of the infants with facial clefts had associated defects. Males predominated for cleft lip; females for cleft palate. Cleft lip (alone) was more common in babies born to women aged 35 years and over. Sudden declines in registered prevalence were observed in 1978 and 1985. Clefts were more common in socioeconomically deprived areas of the city.

In comparison with data from elsewhere, Glasgow seems to have a low rate of cleft lip, a high rate of cleft palate, and a high rate of associated defects. Many of the findings of cleft palate in Glasgow could be explained by the interaction of an unidentified environmental teratogen with a susceptible population.

In the continued absence of an understanding of their aetiology, the epidemiological investigation and monitoring of facial clefts remain important both from a research and public health point of view. A recent report from European Registration of Congenital Anomalies and Twins (EUROCAT) suggests that Glasgow has experienced a higher prevalence of cleft palate than any of the other participating centres over the period 1980–83.[1] The purpose of the present study was to attempt to identify possible reasons for this by means of a more detailed investigation of the descriptive epidemiology of facial clefting in Glasgow.

## Methods

All congenital anomalies either identified in a child born (alive or stillborn) to a Glasgow resident or diagnosed in a therapeutically terminated pregnancy of a Glasgow resident, are notified to the Glasgow Register of Congenital Malformations of the Greater Glasgow Health Board Multiple sources of ascertainment are used, including paediatric discharge letters, hospital (including dental hospital) records, health visitors, perinatal conferences, and death registrations There is no formal time limit to the period after birth within which notifications are accepted.

Data on facial clefts were abstracted from the Register for the birth years 1974–85. Information was obtained on the category of facial cleft, any associated defects or syndromes, birthweight, sex, maternal age and postcode sector of maternal residence. The classic epidemiological triad of person, time, and place was analysed for each case.

## Results

**Personal characteristics of infants and mothers.** Over the 12 years 1974–85 there were 158 668 births in the Greater Glasgow Health Board area. Facial clefts were registered in 247 infants (including seven terminations of pregnancy), representing a prevalence of 1·56 per 1000 total births. Of these, more than half (138) were associated with other malformations Cleft palate (alone) occurred almost twice as often as cleft lip (alone), with cleft lip and palate occupying an intermediate position (Table 1) The prevalence of other associated defects varied according to the category of facial cleft: almost two thirds of children with cleft palate had other defects, compared with less than one third of children with cleft lip. Children with cleft lip and palate again occupied an intermediate position, being fairly evenly divided between those who did and did not have other defects. Table 2 shows that the most common association was with the Pierre-Robin sequence in 38 children, all but one of whom had cleft palate. The severity of the associated defects is shown by the fact that only 57% of the infants with

Table 1 *Infants with facial clefts notified to the Glasgow Register 1974–1985 (total births = 158 668)*

| *Category of facial cleft* | *Facial clefts alone* | | *Facial clefts associated with other defects* | | *Total facial clefts* | |
|---|---|---|---|---|---|---|
| | *No* | *Rate/1000* | *No* | *Rate/1000* | *No* | *Rate/1000* |
| Cleft lip | 24 | 0·15 | 9 | 0·06 | 33 | 0·21 |
| Cleft lip and palate | 41 | 0·26 | 44 | 0·28 | 85 | 0·54 |
| Cleft palate | 44 | 0·28 | 85 | 0·54 | 129 | 0·81 |
| All categories | 109 | 0·69 | 138 | 0·87 | 247 | 1·56 |

Table 2 *Congenital malformations associated with facial clefts*

| *Associated malformations* | *No* | *%* |
|---|---|---|
| Pierre-Robin sequence | 38 | (28) |
| Musculoskeletal defects | 25 | (18) |
| Neural tube defect | 21 | (15) |
| Chromosomal defects | 14 | (10) |
| Cardiovascular defects | 10 | (7) |
| Others (including syndromes) | 30 | (22) |
| Total | 138 | (100) |

Table 3 *Sex ratio of registered cases of facial clefts, 1974–1985*

| *Category of cleft* | *No M* | *F* | *Sex (M/F) ratio* |
|---|---|---|---|
| Cleft lip only | 18 | 6 | 3:1 |
| Cleft lip and palate only | 34 | 7 | 4·9:1 |
| Cleft palate only | 17 | 27 | 1:1·6 |
| Cleft lip with other defects | 7 | 2 | 3·5:1 |
| Cleft palate with other defects | 33 | 52 | 1:1·6 |
| Cleft lip and palate with other defects | 25 | 18 | 1·4:1 |

them were alive at aged 1 year, compared with 84% of those with facial clefts alone.

There was a pronounced male predominance for cleft lip and for cleft lip and palate, but a female predominance for cleft palate (Table 3)

The prevalence of low birthweight (less than 2500 g) in infants with facial clefts was 13%, almost double the figure (7%) for all Glasgow births during the period 1975–84 (Forbes JF, personal communication), and was particularly high (26%) in infants with both cleft lip and cleft palate.

The only association with maternal age was found in babies born to women aged 35 years and over in whom the prevalence of both cleft lip (alone) and cleft palate (alone) seemed to be higher than in the younger age groups. The difference was, however, significant (at the 5% level) only for cleft lip.

**Time trends.** During the period studied there were two sharp dips in prevalence. The first, in 1978, was entirely confined to cleft palate (with or without cleft lip), while the second, in 1985, concerned all three categories (Table 4). The decline in 1978 is likely to have been real as the number of infants attending the Glasgow Dental Hospital with facial clefts was also unusually low at that time. (1985 dental data were not yet available at the time of writing). There was one other notable trend: the incidence of clefts associated with other malformations rose over the study period, particularly after 1979, while the prevalence of clefts unassociated with other malformations declined (Table 5).

Table 4 *Annual prevalence (per 1000 total births) of facial clefts (with or without associated malformations) in Glasgow, 1974–1985**

| *Year* | *Cleft lip* | | *Cleft lip and palate* | | *Cleft palate* | | *All clefts* | |
|---|---|---|---|---|---|---|---|---|
| | *No* | *Rate* | *No* | *Rate* | *No* | *Rate* | *No* | *Rate* |
| 1974 | 7 | 0·5 | 10 | 0·7 | 10 | 0·7 | 27 | 1·8 |
| 1975 | 3 | 0·2 | 8 | 0·6 | 11 | 0·8 | 22 | 1·5 |
| 1976 | 1 | 0·1 | 10 | 0·8 | 10 | 0·8 | 21 | 1·6 |
| 1977 | 1 | 0·1 | 8 | 0·6 | 10 | 0·8 | 19 | 1·5 |
| 1978 | 2 | 0·2 | 3 | 0·2 | 4 | 0·3 | 9 | 0·7 |
| 1979 | 2 | 0·2 | 5 | 0·4 | 10 | 0·8 | 17 | 1·3 |
| 1980 | 5 | 0·4 | 4 | 0·3 | 15 | 1·1 | 24 | 1·8 |
| 1981 | 2 | 0·2 | 9 | 0·7 | 13 | 1·0 | 24 | 1·8 |
| 1982 | 2 | 0·2 | 6 | 0·5 | 19 | 1·5 | 27 | 2·1 |
| 1983 | 3 | 0·2 | 9 | 0·7 | 9 | 0·7 | 21 | 1·7 |
| 1984 | 4 | 0·3 | 10 | 0·8 | 13 | 1·0 | 27 | 2·1 |
| 1985* | 1 | 0·1 | 3 | 0·3 | 5 | 0·5 | 9 | 0·9 |
| Total | 33 | 0·2 | 85 | 0·5 | 129 | 0·8 | 247 | 1·6 |

*Figures for 1985 are provisional

Table 5 *Annual prevalence (per 1000 total births) of facial clefts (without associated malformations) in Glasgow, 1974–85**

| *Year* | *Cleft lip* | | *Cleft lip and palate* | | *Cleft palate* | | *All clefts* | |
|---|---|---|---|---|---|---|---|---|
| | *No* | *Rate* | *No* | *Rate* | *No* | *Rate* | *No* | *Rate* |
| 1974 | 6 | 0·4 | 8 | 0·5 | 6 | 0·4 | 20 | 1·3 |
| 1975 | 2 | 0·1 | 3 | 0·2 | 6 | 0·4 | 11 | 0·8 |
| 1976 | 1 | 0·1 | 7 | 0·5 | 5 | 0·4 | 13 | 1·0 |
| 1977 | 1 | 0·1 | 7 | 0·6 | 5 | 0·4 | 13 | 1·0 |
| 1978 | 1 | 0·1 | 2 | 0·2 | 2 | 0·2 | 5 | 0·4 |
| 1979 | 1 | 0·1 | 0 | 0 | 0 | 0 | 1 | 0·1 |
| 1980 | 4 | 0·3 | 1 | 0·1 | 4 | 0·3 | 9 | 0·7 |
| 1981 | 1 | 0·1 | 2 | 0·1 | 3 | 0·3 | 6 | 0·5 |
| 1982 | 1 | 0·1 | 3 | 0·2 | 6 | 0·5 | 10 | 0·8 |
| 1983 | 2 | 0·2 | 1 | 0·1 | 2 | 0·2 | 5 | 0·4 |
| 1984 | 3 | 0·2 | 5 | 0·3 | 3 | 0·2 | 11 | 0·8 |
| 1985* | 1 | 0·1 | 2 | 0·2 | 2 | 0·2 | 5 | 0·4 |
| Total | 24 | 0·2 | 41 | 0·3 | 44 | 0·3 | 109 | 0·7 |

*Figures for 1985 are provisional

Analysis of month of birth indicated a low incidence of facial clefts in November. This pattern seemed to have been confined to cleft palate (alone), though significance was not reached. No seasonal trend was observed either for cleft lip or for cleft lip and palate.

**Place of maternal residence.** Table 6 shows the variation of the prevalence of facial clefts within Greater Glasgow subdivided into eight categories of postcode sectors classified and ranked according to housing and social characteristics. The categories were derived by means of a cluster analysis of variables obtained from the 1981 census. The highest rates were observed in area types 7 and 8 (local authority housing with young families, high unemployment, and a preponderance of unskilled workers). The lowest rates were found in area type 1 (professional and non-manual workers in large owner occupied housing with two or more cars) and type 3 (mainly non-manual and professional workers in older but good quality housing) Most of this gradient is accounted for by cleft palate: cleft lip (with or without palate) varied less A similar pattern was found when the analysis was repeated for clefts unassociated with other malformations (Table 7).

Table 6 *Prevalence (per 1000 total births) of facial clefts (with or without associated malformations) in eight types of area within Glasgow, 1974–1985*

| *Housing/social type area* | *Cleft lip with or without cleft palate* | | *Cleft palate* | | *All clefts* | |
|---|---|---|---|---|---|---|
| | *No* | *Rate* | *No* | *Rate* | *No* | *Rate* |
| 1 | 12 | 0 7 | 5 | 0 3 | 17 | 1 0 |
| 2 | 12 | 0 7 | 15 | 0 9 | 27 | 1 6 |
| 3 | 6 | 0 4 | 8 | 0 6 | 14 | 1 0 |
| 4 | 12 | 0 7 | 10 | 0 6 | 22 | 1 3 |
| 5 | 25 | 0 8 | 23 | 0 8 | 48 | 1 6 |
| 6 | 9 | 0 8 | 10 | 0 9 | 19 | 1 8 |
| 7 | 18 | 0 9 | 28 | 1 4 | 56 | 2 2 |
| 8 | 24 | 0 9 | 30 | 1 1 | 54 | 2 0 |
| Total | 118 | 0 8 | 129 | 0 8 | 247 | 1 6 |

Table 7 *Prevalence (per 1000 total births) of facial clefts (without associated malformations) in eight types of area within Glasgow, 1974–85*

| *Housing/social type area* | *Cleft lip with or without cleft palate* | | *Cleft palate* | | *All clefts* | |
|---|---|---|---|---|---|---|
| | *No* | *Rate* | *No* | *Rate* | *No* | *Rate* |
| 1 | 5 | 0 3 | 1 | 0 1 | 6 | 0 4 |
| 2 | 6 | 0 4 | 4 | 0 2 | 10 | 0 6 |
| 3 | 3 | 0 2 | 0 | 0 | 3 | 0 2 |
| 4 | 9 | 0 6 | 2 | 0 1 | 11 | 0 7 |
| 5 | 14 | 0 5 | 6 | 0 2 | 20 | 0 7 |
| 6 | 3 | 0 3 | 5 | 0 5 | 8 | 0 8 |
| 7 | 10 | 0 5 | 11 | 0 5 | 21 | 1 0 |
| 8 | 15 | 0 6 | 15 | 0 5 | 30 | 1 1 |
| Total | 65 | 0 4 | 44 | 0 3 | 109 | 0 7 |

## Discussion

A recent prospective epidemiological study of facial clefting was reported from Liverpool,[2] a city which is, in many ways, comparable with Glasgow. Both cities have operated registers of congenital anomalies for several years and both are participants in the multicentre EUROCAT project. The Glasgow Register enjoys the advantage of having been subjected to a systematic evaluation of the accuracy and completeness of its data for the earlier years (1972–77) of its operation. At that time the Register successfully ascertained about two thirds of all known infants with oral clefts (Stone DH, Evaluation of A Register (Report for Mastership, Faculty of Community Medicine Part 2), 1979)

The overall prevalence of facial clefts is similar in the two cities and is compatable with the results of other studies.[3] The distribution of the types of defects within the total prevalence, however, varies In Glasgow more than half of the defects are cleft palate and slightly less than half are cleft lip (with or without cleft palate) In Liverpool only about a third of the defects are cleft palate, most being cleft lip (with or without cleft palate). The Liverpool pattern is closer to that reported from other studies in which a predominance of cleft lip (with or without cleft palate) is the norm, suggesting that the Glasgow figure for the prevalence of cleft lip may be an underestimate.

Glasgow is also atypical in another way. The majority of children with facial clefts had associated defects, most of which were serious in terms of the lesions themselves and the survival of the affected infants. Liverpool reported that only 16% of the children with facial clefts were associated with 'more than one other major anomaly,' and while it is possible that the Liverpool rate of associated defects would have been much higher had children with only one associated defect been included, the Glasgow figure does seem to be unusually high.[1 3]

In both Glasgow and Liverpool there was an excess of males with cleft lip (with or without cleft palate), but this was not the case for cleft palate, which showed either a female predominance (Glasgow) or no predominance (Liverpool), confirming the general trend observed elsewhere.[3 4] The higher prevalence in babies born to older mothers observed in Glasgow has also been described elsewhere [3 4] Seasonality has been inconsistently reported, and there is little in common between Glasgow and Liverpool in this respect except for an apparent absence of any seasonal trend in prevalence of cleft lip.

A real decline in the prevalence of facial clefts took place in Glasgow in 1973, but not in Liverpool, where if anything, an increase in prevalence occurred at that time Thereafter, the predominance of clefts associated with other malformations in Glasgow may have been due to improved ascertainment in the wake of the findings of the evaluation exercise which was reported in 1979. Alternatively, both the differing secular trends in the two cities and the changing relative incidence of clefts associated and unassociated with other defects in Glasgow may reflect some unidentified environmental teratogen that was waxing and waning at different times in the two locations.

The possibility of an association with epilepsy and anticonvulsant treatment cannot be excluded as neither study collected sufficient data on the subject, but only 3% of the Liverpool cases were associated with a maternal history of epilepsy, which could therefore explain only a small proportion of the prevalence.

Social class distribution was not reported by either study but the Glasgow finding of an association between cleft palate and areas of socioeconomic deprivation suggests either that a teratogenic factor may be more prevalent in such areas, or that a deprived environment enhances the susceptibility of the population to a specific teratogen. An interaction between low socioeconomic status or a poor environment with such a teratogen could explain Glasgow's high prevalence of cleft palate, as well as the variable seasonal, secular, and geographical patterns of reported prevalence. The nature of the specific teratogen remains a matter of speculation, but diet, infection, and drugs are all worthy of continued scrutiny.

We thank Dr Frances Hamilton and Mr T Sinclair for their invaluable help without which this work could not have been performed

Glasgow is one of the British participating Centres in the EUROCAT project

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# Cardiorespiratory patterns in siblings of babies with sudden infant death syndrome

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SUMMARY Clinical data and 24 hour tape recordings of electrocardiogram (ECG) and abdominal breathing movements were collected from 301 infants who had had a sibling who had suffered the sudden infant death syndrome (SIDS). Of these, 261 were referred cases, and 40 were recorded prospectively as part of a population based study; none of the 301 subsequently died. Fifty five of the referred siblings who had been born at full term (⩾37 week gestation) were randomly selected for a detailed analysis of heart rate and breathing patterns, as were all siblings born at full term from the prospective study (16 with a previous sibling in whom SIDS had occurred and seven with a sibling born at full term and in whom SIDS had subsequently occurred). The control group consisted of 197 recordings on 170 infants born at full term and matched by postnatal age.

The mothers of the siblings smoked and consumed alcohol more often during pregnancy than the mothers of control babies. The siblings had lower Apgar scores and were more often breast fed than controls.

There were no significant differences in the number of apnoeic pauses in the quantities of periodic breathing or in the heart and respiratory rates during regular breathing between the siblings and the controls.

In seeking to understand the pathophysiology of SIDS the subsequent siblings of cases of SIDS provide an easily accessible group for study A recent population based epidemiological study, however, has shown that their individual risk is low and it seems unlikely that the investigation of small numbers of infants who have lost a sibling to SIDS will provide helpful information.[1] Papers have been published describing higher respiratory rates in subsequent siblings than in controls,[2-3] while others have failed to reproduce these findings.[4-5] Some of the reports we studied described more short apnoeic pauses in subsequent siblings;[6-9] others reported fewer in this group [2] Although Kelly *et al*[10] reported more examples of periodic breathing in siblings, this was not confirmed by Flores-Guevara *et al.*[7]

In an attempt to resolve these conflicting findings we analysed heart rate and breathing patterns on 24 hour tape recordings of ECG and abdominal breathing movements on 78 siblings of cases of SIDS who had been born at full term (⩾37 weeks' gestation), and 170 age matched controls who had also been born at full term. We also include a comparison of prenatal and early postnatal clinical data between these 78 siblings and their 170 controls.

## Patients

**Controls.** A total of 197 24-hour tape recordings of ECG and abdominal wall movements were performed on 170 control infants. These infants were born at one of four hospitals, were born at full term (⩾37 weeks' gestation), and were chosen to cover the same age range as the siblings A proportion was from a previously reported sequential control group;[11] a second group was randomly selected from surviving infants being studied as part of a prospective investigation into SIDS;[12] and a small group of older infants was chosen randomly from a local health visitors' clinic in Doncaster.

Prenatal and early postnatal clinical data were compiled from hospital notes and questionnaires given to parents at the time of the recordings. Four of the 170 controls were from twin pregnancies. Social class was assessed according to the employment of the major wage earner in the family [13] The social class of the control group (but not the siblings) was compared with national statistics from the 1981 census to check that they were representative.[14]

**Siblings of cases of SIDS:** A total of 301 siblings were studied, all of whom were followed up from the England and Wales central death register based at the Office of Population Censuses and Surveys.

The subgroup undergoing comparison with the control group consisted of 78 cases chosen from two sources. Fifty five cases were referred for clinical assessment (45 by consultant paediatricians, four by family practitioners, and six by parents), and 23 were part of a prospective population based study of SIDS.[12] The 55 referred cases were randomly selected from the subgroup born at full term of the 261 cases referred to the Brompton Hospital over four years. The remaining 23 comprised the cases born at full term from the population based study; there were 17 babies born preterm who were not studied.[12] This group of 23 was subdivided into 16 with a previous sibling who had had SIDS and seven in whom follow up of the family showed the sudden unexplained death of a subsequent sibling.

Five infants were twins of an infant who had had SIDS; the remainder were single births Six of the referred cases and one of the population based group had more than one previous sibling who had died as a result of SIDS; one of the referred cases had had three previous siblings die of SIDS.

Of the 78 cases of SIDS whose siblings we studied physiologically, 61 deaths were verified as SIDS by necropsy reports from coroners or pathologists. In 17 cases summaries from the hospitals referring the siblings stated that SIDS was the cause of death, but it was not possible to obtain copies of necropsy reports.

The physiological data comprised 89 recordings: 59 on the 55 referred cases, 21 on the 16 population based group in which a previous sibling had died; and nine on the seven population based group in

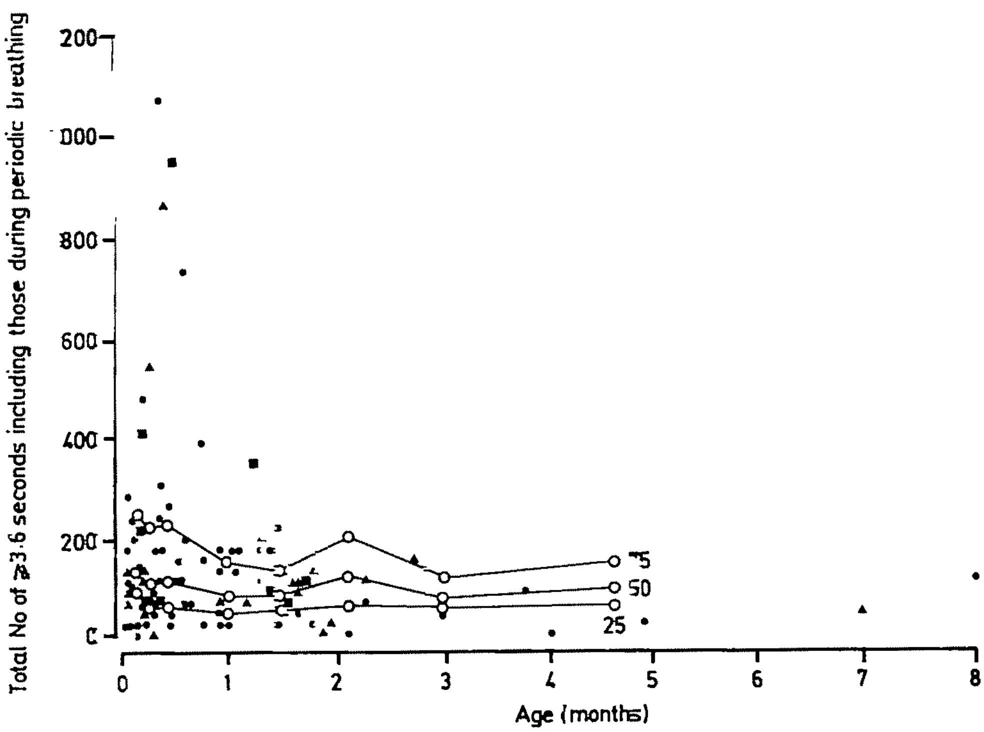

Fig 1 *Total No of apnoeic pauses for recording plotted against postnatal age For controls, 25th, 50th, and 75th group centile values are plotted at median age of each group Values for apnoeic pauses on each individual recording for each sibling are plotted at age of first recording:* ●=*siblings referred for investigation,* ▲=*population based cases recorded after previous sibling had died of SIDS* ■=*population based cases recorded before future sibling had SIDS*

which a future sibling died. Clinical data comparable with those for the control group were collected on the 78 cases.

## Methods

All recordings in cases and controls contained more than 18 hours of adequate breathing movement and heart rate signals. Full details of the recording and analysis procedures used in the study have been reported previously.[11] In summary, a 24 hour tape recording of ECG and abdominal wall movements, the latter from a pressure capsule transducer, was performed on each sibling and each control.

Recordings on the siblings were performed either in the hospital ward or, in most cases, at home; the recorder was sent home with the infant and returned 24 hours later. Only 3% of controls underwent recordings in hospital.

Each recording was printed on to chart paper, as described in our previous report,[11] and then measured and analysed blind by three technicians. The variables measured are listed below

The number of apnoeic pauses $\geq$3·6 seconds in duration per recording were counted and categorised according to their duration—that is, $\geq$3·6–6·0 seconds and >6·0–12·0 seconds, and the duration of the overall longest pause per recording was also measured Periodic breathing and periodic apnoea were defined as reported earlier,[11] and the total duration of each and the longest single episode of periodic breathing were measured for each recording. Regular breathing was also defined as reported earlier[11] but a more stringent definition was adopted for this measurement. Both heart and respiratory rates were measured over periods of one minute during each episode of regular breathing, avoiding pauses and sighs, and an average taken for the

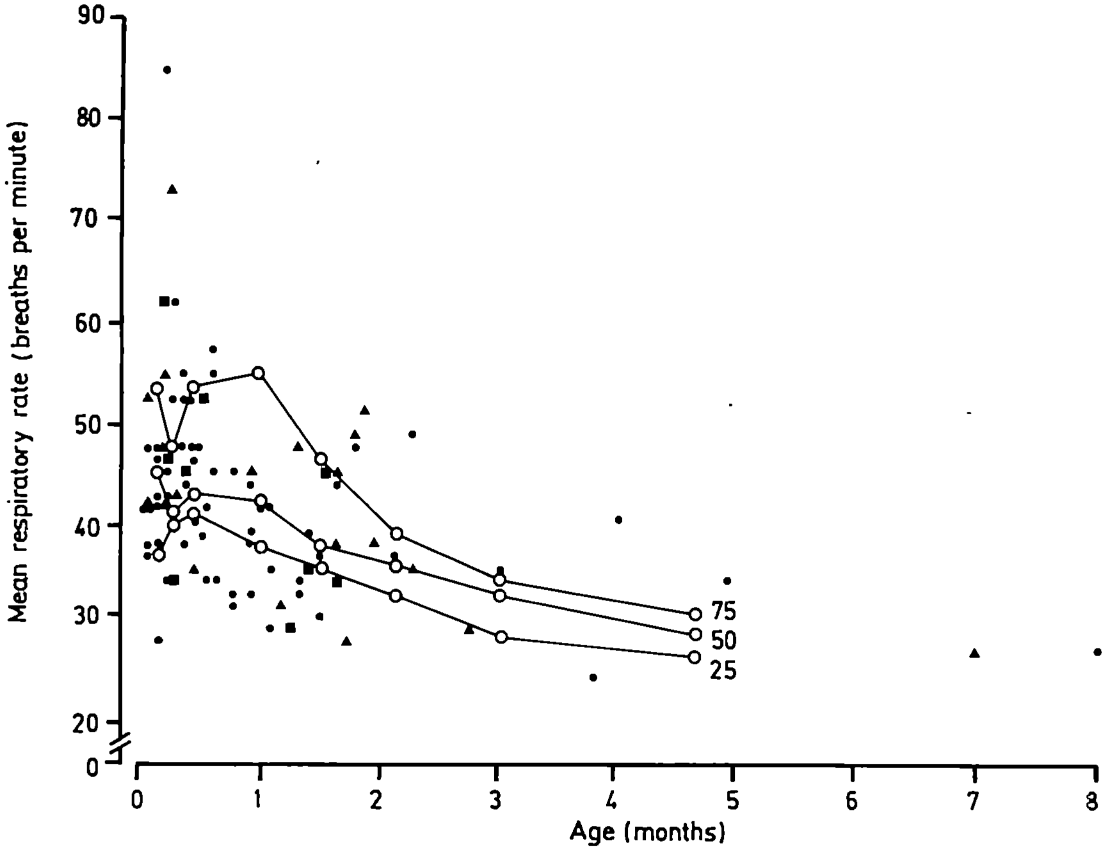

Fig. 2 *Mean respiratory rate during regular breathing for each recording plotted against age at time of recording For controls, 25th, 50th, and 75th group centile values are plotted at median age of each group Values for apnoeic pauses on each individual recording for each sibling are plotted at age of that recording ●=siblings referred for investigation, ▲=population based cases recorded after previous sibling had died of SIDS; ■=population based cases recorded before future sibling had SIDS.*

whole recording Where appropriate, measurements were adjusted to account for artefact and varying lengths of recording, to a nominal 22 hours (the average).

Comparison of clinical data on siblings and controls was by Student's t test, Fisher's exact test, or the $\chi^2$ test, as appropriate.

Comparison of physiological data on siblings and controls was by the Van-Elteren modified Wilcoxon rank sum test for stratified data.[15]

The following 15 clinical variables were compared between cases and controls: for each mother her age at the time of the birth, the social class of her family, her smoking and alcohol consumption during pregnancy, any serious medical problems or complications of the pregnancy, any medication taken during pregnancy and the mode of delivery of her infant; and for each infant the Apgar scores at one and five minutes, sex, gestational age and birth weight, the reception of resuscitation at birth, and mode of feeding at the time of recording.

## Results

A comparison of clinical variables showed that the mothers of siblings smoked and consumed alcohol more often during pregnancy ($p<0{\cdot}01$ and $p<0{\cdot}05$, respectively). The mothers of siblings more often had a history of serious medical problems ($p<0{\cdot}05$) but took less medication during pregnancy ($p<0{\cdot}05$). Compared with controls there was no difference in birth weights or Apgar scores at one minute, but more of the sibling cases were breast fed ($p<0{\cdot}01$). At five minutes the Apgar scores were lower in siblings ($p<0{\cdot}05$). A comparison of occupational origins of the siblings with controls and those of controls with the general population showed no significant differences.

When measurements of apnoeic pauses, periodic breathing, regular breathing, and heart and respiratory rates during regular breathing were compared between siblings and controls, siblings tended to have more short apnoeic pauses and higher respira-

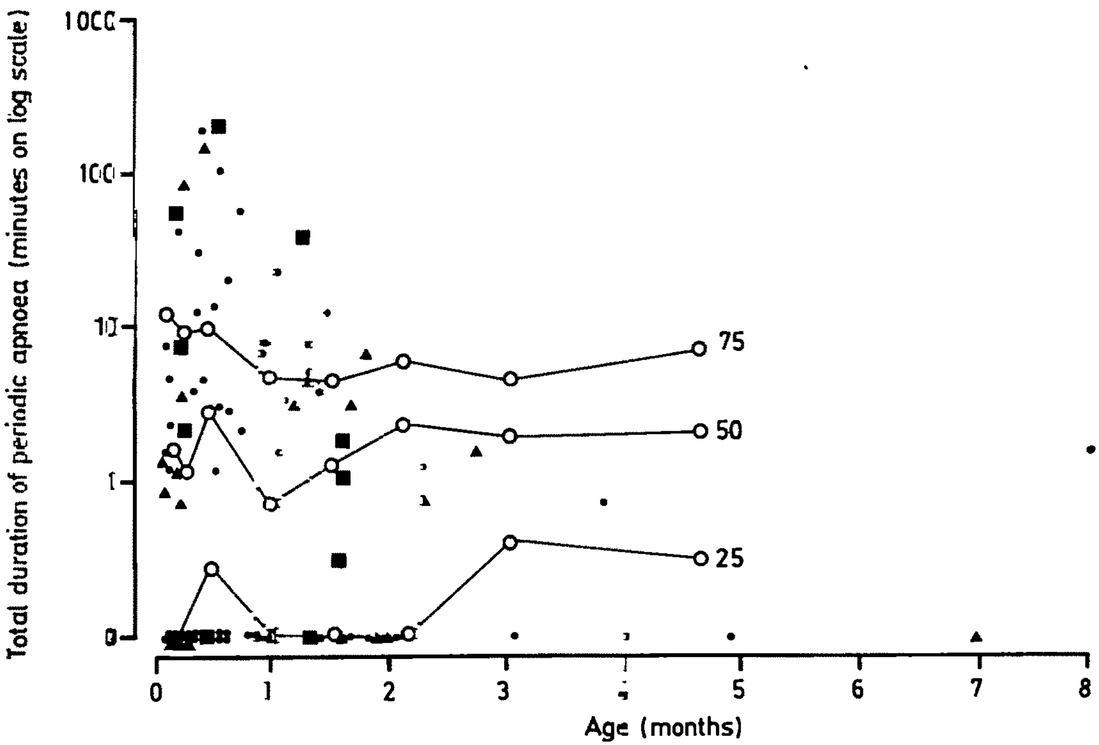

*Fig. 3 Total duration of periodic apnoea per recording on a logarithmic scale is plotted against age at time of recording For controls, 25th, 50th, and 75th group centile values are plotted at median age of each group. Values for apnoeic pauses on each individual recording for each sibling are plotted at age of that recording. ●=siblings referred for investigation, ▲=population based cases recorded after previous sibling had died of SIDS; ■=population based cases recorded before future sibling had SIDS*

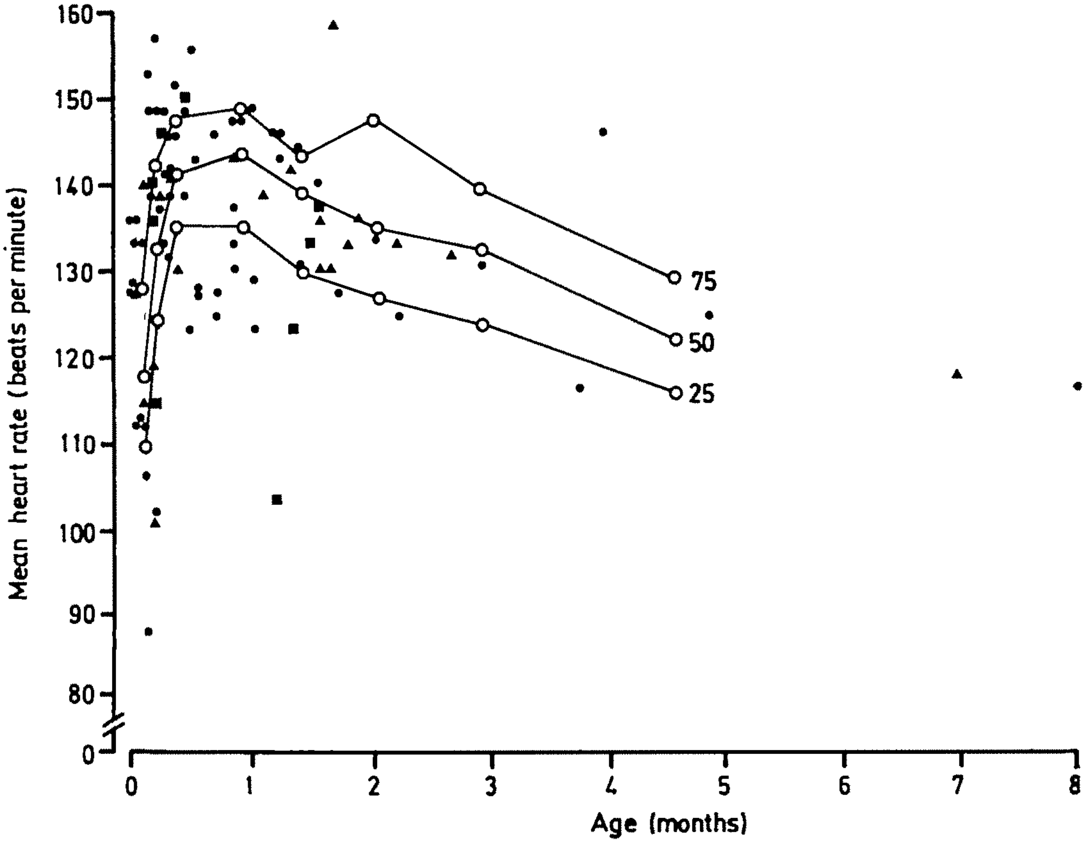

Fig. 4 *Mean heart rate during regular breathing for each tape recording plotted against age at time of recording. For controls, 25th, 50th, and 75th group centile values are plotted at median age of each group Values for heart rate on each individual recording for each sibling are plotted at age of that recording ●=siblings referred for investigation; ▲=population based cases recorded after previous sibling had died of SIDS, ■=population based cases recorded before future sibling had SIDS*

tory rates than controls (Figs 1 and 2). These apparent differences were not, however, significant ($p>0\cdot05$), nor were the levels of periodic breathing or quantities of regular breathing, or heart rates during regular breathing, significantly different between siblings and controls ($p>0\cdot05$) (Figs. 3 and 4).

## Discussion

This study has failed to show any group differences between siblings of cases of SIDS and controls in the quantities of periodic or regular breathing and measurements of apnoeic pauses or heart and respiratory rates during regular breathing.

Our findings concerning respiratory rates complement those of Curzi-Dascalova *et al*,[4] who found no significant group differences and showed a wide variability in values.

Although we have been unable to confirm the results of Hoppenbrouwers *et al*[2] and Carse *et al*,[3] who found higher respiratory rates in siblings, our results do not contradict theirs and, particularly at the younger ages, our siblings showed a tendency in this direction. We did not, however, find any evidence to support the conclusions of Harper *et al*[16 17] that the heart rate is increased in siblings. We consider that the most likely explanation for this discrepancy lies in the wide variability in heart rates in normal infants. A second possibility is that the regular breathing state may not be concordant with quiet sleep.

Kelly *et al*[10] reported increased levels of periodic breathing and, in active sleep, increased numbers of apnoeic pauses[6] in subsequent siblings of cases of SIDS. Flores-Guevara *et al*[7] found no differences in periodic breathing and Hoppenbrouwers *et al*[2] reported reduced numbers of apnoeic pauses in indeterminate sleep in siblings We could not show any significant group differences in these variables although, in the recordings made soon after birth, the siblings seemed to have had slightly larger numbers of short apnoeic pauses.

One group of interest in our study was that of infants from the prospective study whose subsequent siblings had SIDS. At the time of their recordings the parents were unaware that their infant's future sibling was at increased risk of subsequent SIDS. Although this particular group was relatively small, no difference in the physiological variables was identified between the latter and those cases where a previous sibling had died of SIDS.

Smoking and alcohol intake during pregnancy and serious maternal medical problems were more prevalent in siblings of SIDS babies than in controls. Some of these variables have been previously noted to be overrepresented in mothers of infants who had SIDS.[18]

In conclusion, the analyses we have performed on heart rate and breathing movement patterns in this group of siblings of cases of SIDS failed to identify measurements which distinguish them from normal infants Perhaps this is not surprising in view of the small magnitude of increased risk of SIDS in this group of infants[1] and the failure of this particular kind of analysis to predict SIDS in a prospective population based study.[19]

We are grateful to the Foundation for the Study of Infant Deaths (FSID), Healthdyne, Smith's Charity Dr Southall was supported by the British Heart Foundation, the Waring Scholarship, Healthdyne, the National SIDS Foundation, Nellcor, the Joseph Levy Foundation, Valerie Stebbens was funded by FSID and the Nuffield Foundation We thank Pauline Mills, Jackie Kelly, and Wendy Yates who made the primary measurements on the physiological data, and Katy Sewton who typed the manuscript

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# *Short reports*

## Duration of antibiotic courses for neonates

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SUMMARY A survey of the use of antibiotics in a neonatal unit for two years showed a considerable reduction in the mean duration of courses prescribed without any appreciable change in morbidity.

Because of their relative immunodeficiency neonates are highly susceptible to bacterial infection. Signs of sepsis are often non-specific. Thus there must be a low threshold for prescribing antibiotics. Courses of longer than 72 hours have been associated with increasing colonisation by potentially pathogenic Gram negative bacteria[1] It is customary to complete a course of antibiotics lasting several days to minimise the risk of emergence of resistant organisms. Recent evidence however, suggests, that the opposite is true: resistant organisms are more likely to be selected the longer antibiotics are continued.[2] It would be rational, therefore, to stop antibiotics after 48 to 72 hours if no organisms are grown on culture.

### Methods

On 1 May 1984 we began a prospective survey of all antibiotics prescribed to babies with systemic sepsis in the neonatal unit at this hospital. When sepsis was suspected, a surface swab and samples of blood, urine, and cerebrospinal fluid were sent for culture An $x$-ray of the chest was taken and antibiotics were started. Results of cultures were reviewed after 48–72 hours and if no organisms were grown, and the $x$-ray did not suggest pneumonia, antibiotics were stopped. Pneumonia was treated with antibiotics for five to seven days, septicaemia for at least seven days and definite necrotising enterocolitis for 10 days. Necropsy, including histological examination of meninges and lungs, was performed on over 90% of the babies who died. Blood was then taken for culture if it had not been taken previously

We present the results of the first two years of the survey. Statistical analysis was by Student's $t$ test, the data on the number of days' treatment having been converted to achieve a normal distribution, and analysis of the significance of differences in proportions was by the $\chi^2$ test.

### Results

The Figure and Table show that the total weight of antibiotics used in six month periods decreased after the first six months of the survey This was initially due to a smaller number of babies being given antibiotics. Over the two years, however, there was no significant change in the proportion of babies prescribed antibiotics. The decrease in their use was not due to the fact that smaller babies received antibiotics, as the weight of antibiotics used per baby-day fell concurrently. The population did not change over the two years; there were no changes in admission policy and the birthweight distribution was similar over the four six month periods ($\chi^2=19\cdot5$, 15df, $p>0\cdot1$).

The most noticeable change in prescribing habit was that the median duration of courses of antibiotics decreased progressively and there was a highly significant fall in the mean duration of courses between the first and second years of the survey

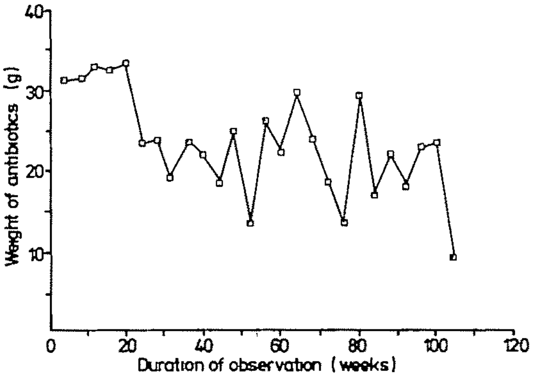

Figure *Grams of antibiotics used in four week periods from 1 May 1984 to 30 April 1986*

Table *Antibiotics in neonatal unit (1 May 1984 to 30 April 1986)*

| | *May 84–October 84* | *November 84 April 85* | *May 85 October 85* | *November 85 April 86* | *P value* |
|---|---|---|---|---|---|
| Baby-days on neonatal unit | 4368 | 3994 | 4383 | 3872 | |
| Cases of late onset sepsis | 4 | 8 | 12 | 4 | NS |
| Weight of antibiotics (g) | 202 7 | 131 7 | 156 6 | 122 1 | |
| Weight of antibiotics per baby-day (mg) | 46 4 | 33 0 | 35 7 | 31 5 | |
| Proportion of babies given antibiotics (%) | 57 7 | 42 5 | 37 3 | 45 5 | NS |
| Mean (SD) duration of antibiotic course per days | 5 45 (4 34) | 5 59 (3 66) | 4 74 (4 36) | 3 61 (4 62) | |
| | *May 84–April 85* | | *May–April 86* | | |
| Mean (SD) duration in days of course | 5 51 (3 89) | | 4 25 (4 50) | | <0 0001 |

There was no significant change in the incidence of late onset sepsis (septicaemia or bacterial meningitis after 48 hours) nor was there any increase in mortality from any form of sepsis. No blood cultures grew organisms after antibiotics had been stopped, and no baby developed an infective illness within 48 hours of discontinuing antibiotics. No significant effect on antibiotic resistance of organisms colonising babies or causing infections was found.

## Discussion

Others have attempted to reduce the proportion of babies receiving antibiotics by identifying those that are septic. A significant reduction has been described using a 'sepsis screen,' comprising several rapid laboratory tests.[3] It may, however, be just as important to shorten the duration of courses of antibiotics in babies who do not have infective illness, as those given antibiotics for more than 72 hours are likely to become colonised with virulent Gram negative organisms.[1] Such a practice is likely to be safe as 96% of blood cultures from bacteraemic neonates grew organisms within 48 hours and 98% within 72 hours.[4]

The number of false negative blood cultures is unknown, but most neonatologists have cared for babies with a clinical picture typical of early onset group B streptococcal sepsis or listeriosis who were heavily colonised with the organism but whose blood cultures were sterile. Under these circumstances we would assume that the result was a false negative probably due to the small size of the inoculum in neonatal blood cultures, and would continue antibiotics for seven or more days as we have for confirmed sepsis. Our study shows that antibiotics can be stopped after two to three days, when cultures are negative, without apparently increasing morbidity. The intensive surveillance of sepsis and antibiotic use was probably at least partly responsible for the reduction in the mean duration of courses of antibiotics because medical staff were continually reminded to review the need for antibiotics.

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# Oral mannitol in control of fluid balance

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SUMMARY Oral mannitol 40 g/m$^2$ was given as 5·5% and 20% solutions to six dialysed children. Both solutions caused diarrhoea. Body weight showed no significant change after the 5·5% solution, which may be used as a 'free drink', but fell by 19·8 g/g mannitol after the 20% solution.

Patients with chronic renal failure treated by dialysis must often restrict their fluid intake. Children find this restriction one of the most difficult aspects of treatment by dialysis, particularly if dialysis was preceded by a phase of polyuria. As a result many children experience episodes of fluid overload, which may have fatal consequences. Fluid removal by dialysis may be slow to begin and we have found that oral administration of 20% mannitol is effective for the rapid removal of body water through the gastrointestinal tract.

## Patients and methods

Six children aged 9 to 16 participated in the study. Two were on haemodialysis and the other four were on continuous ambulatory peritoneal dialysis (CAPD). All except one were fluid restricted to 300–600 ml daily and all found this difficult to accept. The purpose of the study was explained to the children and consent given by their parents.

Five of the children were admitted for the day and were given a standard dose of mannitol (40 g/m$^2$), flavoured with orange juice as a 5·5% solution (osmolality 302 mOsm/l) on the first occasion and as a 20% solution (osmolality 1099 mOsm/l) on the second, to drink over one hour. The sixth child was given 20% mannitol therapeutically when he was admitted with fluid overload. Each child was weighed on admission and at discharge, after drainage of dialysis fluid for those children on CAPD. All food and fluids were weighed and all stools and urine collected and weighed. CAPD was continued as usual and the input and output recorded. The weight loss attributable to the mannitol was calculated as the difference between the weights on admission and discharge corrected for insensible loss, food and fluid intake, urine output, and fluid balance from CAPD.

Blood was taken for measurement of sodium, potassium, and magnesium concentrations, osmolality, and packed cell volume on admission and discharge. The packed cell volume was also measured at 30, 60, 120, and 240 minutes. The pulse and blood pressure were recorded hourly. The patients went home six hours after taking mannitol, by which time the osmotic diarrhoea was abating. The parents kept a record of the number of stools passed for the rest of the day.

The significance of differences was tested by the Mann-Whitney rank sum test.

## Results

Both solutions of mannitol caused diarrhoea of

Table *Effect of treatment with 5% and 20% mannitol solutions on weight loss in six patients on dialysis*

| *Case No* | *Diagnosis* | *Body weight (kg)* | *Dialysis* | *Mannitol* | | *Weight of stool (g)* | *Weight loss* | |
|---|---|---|---|---|---|---|---|---|
| | | | | *Concentration (%)* | *Dose (g)* | | *(g)* | *(g/kg)* |
| 1 | Urethral valves | 30·9 | HD | 5·5 | 41·2 | 675 | 26 | 0·84 |
| | | 30·5 | | 20 | 41·2 | 883 | 126 | 4·13 |
| 2 | Haemolytic uraemic syndrome | 23·1 | CAPD | 5·5 | 34·5 | 240 | +36 | +1·56 |
| | | 23·0 | | 20 | 34·5 | 147 | 361 | 15·7 |
| 3 | Focal segmental glomerulosclerosis | 19·4 | CAPD | 5·5 | 30·3 | 722 | 210 | 10·8 |
| | | 19·4 | | 20 | 30·3 | 602 | 587 | 30·3 |
| 4 | Henoch-Schönlein nephritis | 33·0 | CAPD | 5·5 | 11·6 | Lost | +100 | +3·03 |
| | | 33·4 | | 20 | 29·4 | 1234* | 737 | 22·1 |
| 5 | Reflux nephropathy | 26·4 | CAPD | 5·5 | 36·2 | 622 | 380 | 14·4 |
| | | 25·0 | | 20 | 23·6 | 346 | 620 | 24·8 |
| 6 | Urethral valves | 41·5 | HD | 20 | 51·6 | 920 | 1046 | 25·2 |

*Urine mixed with stool

HD=Haemodialysis; CAPD=continuous ambulatory peritoneal dialysis similar volume that began one to two hours after ingestion. Nausea prevented one patient from taking the full dose of 20% mannitol and another vomited after taking both solutions. The actual dose retained was calculated after measuring the vomitus. The other patients drank the solution without difficulty. One patient opened her bowels into the toilet so the stool could not be weighed. Others were unable to keep small amounts of urine separate from the stools. All the day patients who retained the full dose of mannitol passed at least one further loose stool at home, so the amounts of stool and the total weight losses are underestimated

After 20% mannitol the weight loss was 580 ±315 g but after the 5·5% solution was minimal (96±196 g) (Table). Weight loss was related to the dose of mannitol given as 20% solution (median 19·3 g/g mannitol, range 3·1–25·3 g/g mannitol), but the effect was obscured by case 1 who lost only 126 g despite passing 883 g of stool and who may have taken additional unrecorded fluid. The use of 20% mannitol in case 6 rendered an emergency haemodialysis unnecessary.

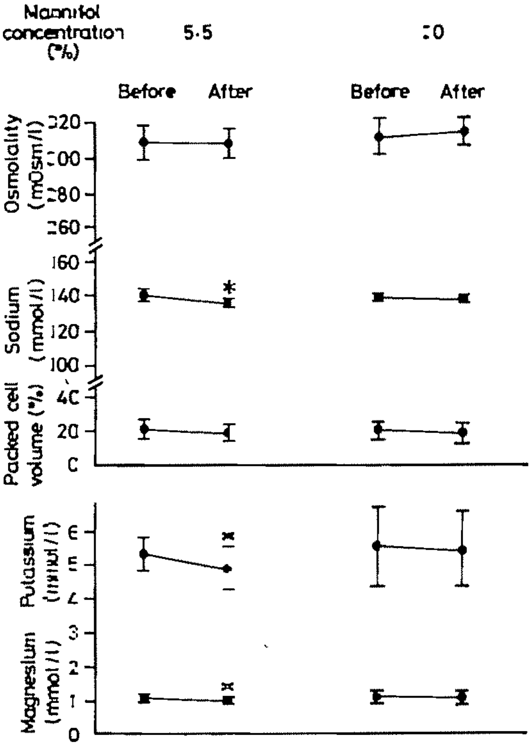

Figure *Changes in blood constituents in six patients on dialysis treated by administration of 5·5% and 20% mannitol, showing mean (SD) values*
*p<0·02.

After the 5·5% mannitol solution serum electrolyte concentrations, packed cell volume, and osmolality fell significantly but by clinically unimportant amounts (Figure). Blood constituents did not change significantly after 20% mannitol. Blood pressure and pulse remained stable throughout the study. After the study three patients continued to use 5·5% mannitol as an unrestricted drink, although they disliked the diarrhoea.

## Discussion

Mannitol ($C_6H_{14}O_6$) is a sugar alcohol that is only partially absorbed from the gastrointestinal tract and causes osmotic diarrhoea.[1] It tastes about half as sweet as sucrose. Nasrallah and Iber showed that an average of 17·5% of an oral dose of 20–100 g mannitol given as a 5% solution was recovered in the urine.[2] The absorption depended on the dose given, smaller doses being more completely absorbed. Young *et al* used a 3·28% solution of mannitol and electrolytes for gastrointestinal dialysis in patients with pre-terminal uraemia.[3] Seven litres given over three hours resulted in 7·2% absorption of mannitol. Mannitol is partially metabolised, the remainder being excreted in the urine.[1 2] Oral mannitol has been used in the treatment of oedema in adults,[4] but it has not been reported as part of the regular management of fluid balance in chronic renal failure.

Frequent small doses of mannitol might result in considerable absorption of mannitol and water, which would be removed by CAPD but could accumulate in patients on haemodialysis. The small weight loss observed in three patients after 5·5% mannitol was unexpected but might be explained by loss of faecal material from the bowel.[5] Chronic administration of 5·5% mannitol in large quantities might cause appreciable intestinal malabsorption and electrolyte losses. Nevertheless, we think that these possible disadvantages are outweighed by the benefit of improved compliance that results from the availability of a 'free drink' that carries virtually no risk of fluid overload.

Despite the discomfort of profuse diarrhoea we consider that oral 20% mannitol is a valuable acute treatment for fluid overload in the child with reduced urine output Mannitol may be given in the home or at school or by the district general paediatrician while arrangements are made to transfer the child for dialysis. Further studies are in progress to define the dose-response relation.

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# Brain stem glioma presenting as gastro-oesophageal reflux

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SUMMARY Brain stem gliomas may present as gastro-oesophageal reflux. In such cases gastro-oesophageal reflux presents atypically late, and computed tomography may not detect the presence of the tumour until late in the course of the disease.

Gastro-oesophageal reflux occurs commonly in infants and typically presents with vomiting soon after birth. Respiratory symptoms associated with aspiration, iron deficiency anaemia with oesophagitis, and failure to thrive are, however, well recognised.[1] Gastro-oesophageal reflux may also occur in a variety of disorders of the central nervous system, including cerebral tumours. In these latter disorders the presentation of reflux is often atypical. We describe here three children with brain stem gliomas who presented initially with gastro-oesophageal reflux.

## Case reports

**Case 1.** A boy was born at term, with a birth weight of 3150 g. At the age of 8 months he started to vomit. Investigations yielded no abnormality on chest or skull *x*-ray film, barium meal and follow through examination, jejunal biopsy, repeated midstream urine specimen examinations, metabolic screening, and computed tomography. Cerebrospinal fluid was xanthochromic, but subsequent carotid angiography yielded normal results. Vomiting continued and at 11 months physical examination revealed brisk knee reflexes only, with weight 5·7 kg (<3rd centile), height 72 cm (10th centile), and head circumference 44 cm (3rd centile). A barium meal examination showed a large hiatus hernia with free gastro-oesophageal reflux, and oesophagoscopy showed oesophagitis. A Nissen's fundoplication was performed. After operation the patient developed stridor and signs of a pseudobulbar palsy. Brain scan showed dilatation of the ventricles, with a tumour mass surrounding the fourth ventricle. Despite a ventricular drain, ventilation, and intensive support, the patient's condition continued to deteriorate and he died.

Postmortem examination confirmed the presence of a large tumour, which filled the fourth ventricle and invaded the medulla, pons, and right cerebellar hemisphere. Both the nucleus ambiguus and tractus solitarius were involved. Histology showed a poorly differentiated glioma.

**Case 2.** A boy was born normally at term, with a birth weight of 3300 g. At the age of 4 months he developed attacks of breath holding, but he thrived otherwise. By 9 months he was vomiting and experiencing paroxysms of coughing. Investigations, including barium meal, oesophagogastroscopy, metabolic studies, electroencephalography (EEG), and computed tomography, yielded normal results. His symptoms continued and by 12 months he presented as a thin, wasted child with persistent drooling, absent ankle reflexes, tongue furrowed on the left side, and his neck held in extension. His weight was 7·65 kg (<3rd centile), height 72 cm (3rd centile), and head circumference 46·5 cm (25th centile). Blood pressure was 110/70. All investigations, including auditory evoked responses, EEG, computed tomography, and those for Riley-Day syndrome, produced normal results except a barium meal examination, which now showed a dilated oesophagus with disordered motility.

Vomiting continued and because of the ineffective and poorly coordinated peristalsis a Nissen's fundoplication and pyloroplasty was performed at 15

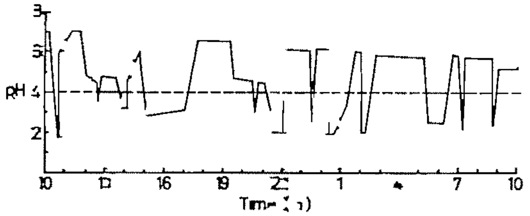

Figure Twenty four hour oesophageal pH study in case 3 Gastro-oesophageal reflux (pH $<4$) was present for 28·5% of the recording.

months. The vomiting resolved after surgery and he started to thrive. His breath holding attacks later became a major problem and at 2·5 years he was reassessed. Neurological examination, a further computed tomogram, and an EEG yielded normal results. The cyanotic attacks and apnoea were thought to be due to severe voluntary breath holding. He died suddenly and unexpectedly at 2 years 11 months. At postmortem examination a tumour was found, involving the upper medulla, invading the floor of the fourth ventricle, and affecting the nuclei of the seventh to 10th cranial nerves. It was shown to be a gangliocytoma.

**Case 3.** This boy was born at term weighing 3500 g. At 3 months episodes of vomiting and choking developed. Examination revealed generalised wasting only. Extensive investigations, including metabolic screening, jejunal biopsy, chest and abdominal *x*-ray films, upper gastrointestinal endoscopy, microlaryngoscopy, and computed tomography, all yielded normal results. His symptoms continued and at 15 months he weighed 7·5 kg (<3rd centile) and had a height of 76 cm (10th centile) and a head circumference of 48 cm (50th centile). Examination produced normal results apart from brisk deep tendon reflexes. A barium meal examination showed a sliding hiatus hernia with gastro-oesophageal reflux, which on 24 hour oesophageal pH study was present for 28·5% of the time (Figure). A midline posterior fossa mass was found on computed tomography. At operation the tumour had infiltrated the floor of the fourth ventricle and extended down the cervical cord to the second cervical vertebra. A subtotal resection of a grade II astrocytoma was performed. The patient is being followed up as an outpatient.

## Discussion

The three patients described here all presented with vomiting due to gastro-oesophageal reflux, but the timing of presentation was atypically late for infantile reflux.

The pathophysiology of gastro-oesophageal reflux is complex and involves a number of factors, including lower oesophageal sphincter tone, oesophageal motility, and gastric emptying. Resting tone in the lower oesophageal sphincter is largely myogenic but is influenced by neural and humoral factors both in an excitatory and inhibitory fashion. The neural component is composed of extrinsic and intrinsic neural elements. The extrinsic element is almost entirely the vagus nerve, which supplies a network of intramural branches to the distal oesophagus and is largely responsible for sphincter relaxation.[2]

The brain stem may therefore modulate oesophageal motility through vagus nerve projections to the oesophagus. The neurophysiological basis for this has been provided by animal studies in which electrical stimulation of brain stem structures, the dorsal motor nucleus of the vagus, and the nucleus ambiguus resulted in dysmotility of the upper gastrointestinal tract in cats.[3] [4] The present cases highlight the clinical relevance of these animal studies and are further strengthened by a recent report of the presentation of a brain stem glioma with disordered motility of the upper gastrointestinal tract.[5] Thus there is both clinical and experimental evidence to support an association between brain stem lesions and disordered oesophageal motility or even hiatus hernia. It has been suggested that the latter is due to contraction of the longitudinal smooth muscle layer of the oesophagus.[6] Thus if there is disordered extrinsic innervation through the vagus nerve this may well by important in the genesis of the hiatus hernia.

Brain stem tumours present insidiously as the tumour infiltrates between normal neural structures, separating rather than destroying them. Obstruction of flow of cerebrospinal fluid occurs late and the diagnosis is usually suggested by the presence of cranial nerve and long tract signs in the absence of signs of raised intracranial pressure.[7]

In the three patients described here we suggest that tumour infiltration of the brain stem resulted in disordered oesophageal motility with consequent gastro-oesophageal reflux. It was important that the presenting symptoms of reflux in these patients was atypically late, with vomiting developing towards the end of the first year of life. Initially, computed tomograms yielded normal results in all patients, and this emphasises that computed tomography rarely provides adequate delineation of the brain stem to exclude a tumour in the early stages.

We thank Professor R O Weller for the neuropathology report on the patient in case 2

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# Prognosis in Guillain-Barré, syndrome

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SUMMARY Clinical recovery started in 23 children with Guillain-Barré syndrome after a mean time of 19 days and to full recovery in 15 was 6·2 months. Long term follow up indicated that 19 with acute onset had completely recovered clinically and three with subacute onset had a chronic relapsing or protracted course.

Guillain-Barré syndrome was described more than a century ago, but little has been written about the long term outcome in children. Subacute presentation, severe or prolonged illness, profound sensory loss, papilloedema, CSF pleocytosis, gross slowing of nerve conduction, and onion bulb formation on nerve biopsy are associated with incomplete recovery [1-3] Most studies deal with adult patients. Eberle *et al*, however, referring specifically to Guillain-Barré syndrome in childhood, found that if 16 days elapsed without improvement after the weakest point was reached there was a 96% probability that recovery would not occur, and if the plateau before improvement lasted longer than 18 days incomplete recovery was almost certain.[2] Because the patients in that study were followed up for a fairly short time and because our experience has been quite different we report the long term outcome in a well defined group of children.

## Patients and methods

We studied patients admitted to our hospital during the period January 1970 to December 1985. They were selected according to recommended clinical criteria: progressive motor weakness affecting more than one limb with or without cranial nerve involvement, arreflexia, and absence of pleocytosis.[4] Twenty four patients (13 male and 11 female aged from 19 months to 13 years (mean age 4 years 7 months)) fulfilled the criteria.

## Results

Twelve patients had had a preceding illness or event, upper respiratory tract infection being the most common (seven cases); the others comprised measles (two cases), mumps (one), infectious mononucleosis (one), and pneumoencephalography for suspected hydrocephalus (one).

Twenty one patients presented acutely (symptoms for three weeks or less before maximum deficit) and three subacutely (symptoms for six weeks or more before maximum deficit). Three patients who presented acutely had the Miller-Fisher variant.[5] At the time of maximum neurological deficit 10 patients suffered muscle weakness in both arms and legs. This was severe in four, who also had weak diaphragms Only one patient required ventilation. Eight patients had evidence that the cranial nerves were affected (facial palsy alone in three and multiple cranial nerves affected in five). Six had evidence of autonomic neuropathy manifested as hypertension (three cases), hypotension (one), cardiac arrhythmia (three), profuse sweating (two), and sphincter disturbance (two). The cerebrospinal fluid (CSF) was examined in all patients at least once. A raised CSF protein concentration (mean 1·6 g/l, range 0·1–6·0 g/l) in the absence of a cellular response (less than 10 cells/field) was found in 22 patients. Two patients had a normal CSF protein concentration, but each had only one examination. Treatment consisted of intensive physiotherapy. One child received corticosteroids, and no patient was treated by plasmapheresis.

One patient (aged 19 months) died from cardiorespiratory arrest due to severe autonomic dysfunction. The time taken from maximum deficit to onset of clinical recovery in the remainder ranged from five to 46 days (mean 19·3 days). Time to full clinical recovery (defined as return to normal activities with normal muscle power and return of deep tendon reflexes) was from 2·5 to 15 months (mean 6·2 months) in 15 cases. Of the remaining patients, six were lost to immediate follow up and two were still arreflexic when discharged from hospital.

Twenty two children were followed up and re-examined. The mean follow up interval was seven years for those presenting during 1970–85 and 9·7 years for those presenting during 1970–80. Nineteen were normal on neurological examination and had not developed any complications. Of the remainder, two had chronic relapsing disease and one a protracted illness. The 19 children who had made a full clinical recovery had all originally presented acutely, whereas the three who presented subacutely had a complicated outcome. One patient presented at 13 years of age having had symptoms for three months. She made an incomplete recovery and had two subsequent relapses when aged 16 and 21. At 28 she had persistent distal weakness in the legs, reduced vibration and proprioception, and absent ankle jerks. Another patient presented at the age of 4 having had symptoms for eight weeks. He recovered in three months but relapsed with distal leg weakness, paraesthesia, and arreflexia three years later. He recovered again, and was normal on neurological examination at the age of 10. The third patient had had symptoms for over three months. She improved slowly but was still undergoing rehabilitation one year after presentation. She was unable to walk independently and had mild weakness of the arms, arreflexia, and sensory deficits in the hands and feet.

## Discussion

With the eradication of poliomyelitis Guillain-Barré syndrome has emerged as the most common cause of acute motor paralysis in children. It has been proposed that the syndrome in childhood has a different natural history and a better prognosis than that in adults.[1] The few available paediatric studies have reported small numbers of patients, who were often selected or reviewed over short periods of time. The children reported in the study of Eberle *et al* consisted of patients referred to a rehabilitation institution.[2] Only one of our patients, who had a protracted illness, required referral to a rehabilitation centre. The total number of patients in our study, although small, is comparable with that in other studies in children. The age and sex distribution, preceding events, and type and severity of disease were similar to those described by others.[2] [6] Treatment was supportive in all patients, with emphasis on padding exposed surfaces to prevent secondary pressure neuropathy. This complication may account for some of the residual deficits in patients whose symptoms and signs are prolonged.[3] One child in our study was treated with corticotrophin, although no benefit was apparent.

On long term follow up all patients who presented acutely had made a complete clinical recovery, although two of these had residual deficits for up to two years. This may account for differences in sequelae in studies conducted over shorter periods. All of the patients who presented subacutely developed chronic complications. Other studies have supported this finding and have shown that a longer time (usually more than three months) to maximum deficit is associated with a risk of relapse or of a protracted course.[3] [4] Patients with chronic relapsing or progressive neuropathy seem to have a variant of Guillain-Barré syndrome that can be defined only by the temporal evolution of the disorder.[4] The mean time to onset of recovery from maximum deficit was 19·3 days in our patients. This was longer than that reported by Eberle *et al.*[2] In addition we found no correlation between the rate of recovery or the severity of the illness and the long term outcome.

We conclude that clinical recovery from acute Guillain-Barré syndrome can be expected in all children provided respiratory failure and autonomic neuropathy are appropriately managed. Recovery may not begin for up to six weeks, and full clinical recovery may take up to seven months after the maximum deficit has occurred. Furthermore, subacute presentation seems to indicate a risk of either chronic relapse or a protracted course.

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# Aetiology of growth hormone deficiency

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SUMMARY A retrospective analysis was performed in an attempt to identify perinatal risk factors for the development of growth hormone deficiency More of the affected children were boys, and their birth weights were significantly lower than those of the national average; there were also considerably more preterm and post-term deliveries among boys.

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The aetiology of idiopathic growth hormone deficiency[1] is multifactorial and there is an increased incidence of traumatic deliveries in affected children.[2 3] This study was undertaken to assess whether this association exists in the United Kingdom, and to attempt to identify other perinatal risk factors.

## Methods

We studied cases of idiopathic growth hormone deficiency successfully submitted to the Health Services Human Growth Hormone Committee between January 1980 and June 1984 from 18 of the 19 regional growth centres in the United Kingdom. Details of affected patients were obtained from the growth hormone request forms then in use. Information abstracted included the age and sex of the patient, date of birth, gestation, mode of delivery, birth weight, heights and ages of parents. Statistical analyses were by the $\chi^2$ and unpaired $t$ tests We used the population perinatal data that were collected for the National Perinatal Epidemiology Unit in association with the Office of Population Censuses and Surveys.[4] Anthropometric data were obtained from national sources.[5]

## Results

We studied 300 children (196 boys and 104 girls) Of these, 275 children had isolated growth hormone deficiency and the remaining 25 also suffered from additional endocrine abnormalities. The mean (SD) age of boys was 10·4 (4·0) years and that of girls 9·3 (4·2).

No significant differences were found between affected children and the averages for the normal population concerning the heights of parents, ages of mothers or modes of delivery. The ratio of boys to girls in the sample was 1·88:1, which was significantly greater than the population ratio of 1·06:1 ($p<0·001$). The gestational age, available for 298 of the children, showed that boys with growth hormone deficiency had significantly more preterm (less than 36 completed weeks of gestation) and post-term (greater than 42 weeks of completed gestation) deliveries than the general population ($p<0·001$); this correlation was not found in girls.

The mode of delivery was started for 287 children. We were unable to examine breech deliveries separately, as the figures for England and Wales were not collated separately and the figures for Scotland, although available, were too small for analysis There was, however, no significant increase in the proportion of instrumental deliveries or caesarean sections in the children deficient in growth hormone.

The birth weights of 290 of the children were recorded. The mean (SD) birth weight of boys was 3·18 kg (0·63) and that for girls 3·15 kg (0·62). If we consider the children delivered at term separately the figures rise to 3·29 kg (0·51) and 3·20 kg (0·47), respectively. Compared with national figures the children deficient in growth hormone who were delivered at term were significantly lighter ($p<0·001$) The 25 children with additional endocrine abnormalities were not significantly different from the remainder of the group.

## Discussion

This is the largest series so far to attempt to relate prenatal and perinatal factors to the subsequent development of growth hormone deficiency. The lack of any significant difference between the study group and the normal population with regard to the mode of delivery implies that the strong relation previously noted between traumatic deliveries and subsequent growth hormone deficiency no longer exists in the United Kingdom.

The higher number of boys suffering from growth hormone deficiency has been noted previously,[1–3] although the ratio of affected boys to girls of 1·9:1 in this study is lower than the previous United Kingdom figure of 4:1,[1] and lower than the accumulated ratio from other studies of 2·8:1.[1] Growth hormone deficiency seems to be more common in boys than girls, but to what extent this is due to the fact that affected boys are more likely to seek medical attention is not clear.

As far as we know the significantly larger number of preterm and post-term deliveries in boys but not girls with growth hormone deficiency has not been described. Boys delivered preterm are more likely to suffer complications of prematurity than girls and, as cerebral hypoxia may damage the hypothalamopituitary tract, this may be another aetiological factor.

Our finding of significantly lower birth weights in children deficient in growth hormone requires further comment. Growth hormone is not thought to have an important role in fetal growth; indeed the previously described birth weights of British[1] and American[6] children with growth hormone deficiency were reported to be normal. The birth weights were, however, those reported by the mother rather than those obtained from birth records, and so they may not be accurate. There does not seem to be any other explanation for these findings as the heights of the parents were similar to those of the general population, and if the cause was placental insufficiency it is difficult to relate it to subsequent growth hormone deficiency. Unfortunately, birth lengths were not available: if these children had been significantly shorter than average this would have implicated growth hormone deficiency as the only aetiological agent rather than low birth weight.

We thank the directors of Growth Centres for permission to study data on their patients

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# Neonatal lupus erythematosus, late onset hypocalcaemia, and recurrent seizures

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SUMMARY A 6 day old infant had neonatal lupus erythematosus manifested by rash, haemolytic anaemia, and hepatosplenomegaly. His mother was asymptomatic until eight months of pregnancy. Between 7 and 10 weeks he had recurrent seizures with hypocalcaemia. Other causes of convulsions were excluded. By 14 weeks various abnormalities had largely disappeared.

Neonatal lupus erythematosus (NLE) is rare, about 100 cases having been reported [1] Its manifestations include rash, congenital heart block, and a variety of haematological and systemic abnormalities.[1] Recently, it has been recognised that Ro (SSA) antibodies, associated with Sjogren's syndrome, systemic lupus erythematosus (SLE), and other connective tissue diseases, are uniformly present in the blood of both infants who have NLE and their mothers who have SLE.[1] This finding has led to a better understanding of NLE. We present a case of an infant with NLE who had recurrent seizures of late onset associated with hypocalcaemia. Such a feature has not been previously reported in NLE.

## Case report

The boy was normally born at term after an uneventful pregnancy to a multigravida mother. His Apgar score was 9 at one minute and birth weight was 3400 g. At birth he had a rash on the face, mainly in the periorbital region, with a few lesions on the trunk, and hepatosplenomegaly. The haemoglobin concentration was 13·9 g/dl and platelet count $30\times10^9$/l. He was given a blood transfusion and referred to this hospital.

The mother had developed an erythematous rash on the face during the eighth month of pregnancy, which had gradually increased. She had no other symptoms and had received no medication. Inquiry disclosed that all of her three previous babies had a rash similar to that of the present infant. The first baby had died at 3 days of age, the cause of death was not known. In the second infant the rash had begun to fade by 4 months and had disappeared over the next few weeks. He died of bronchopneumonia and gastroenteritis at 8 months. The third infant had convulsions at 2·5 months and died. Detailed laboratory investigations had not been carried out in these cases. The mother did not have a history of any important illness, rash, or intake of drugs during her earlier pregnancies.

On examination the baby had well marginated, erythematous, maculopapular, non-scaly lesions, 0·5 cm to 2 cm in diameter, mainly on the forehead and cheeks (Figure), with a few lesions on the trunk The liver (3·5 cm) and spleen (1 cm) were enlarged. His general condition was satisfactory and examination of other systems yielded unremarkable results.

The mother had an erythematous, maculopapular, non-scaly rash on her face in a butterfly distribution. Itching and photosensitivity were absent. Systemic examination showed no abnormality

**Laboratory investigations in the baby.** His haemoglobin concentration was 16·0 g/dl, leucocyte count $21\times10^9$/l, with neutrophils 62%, platelets $120\times10^9$/l, and reticulocytes·20%. Blood film showed evidence of haemolysis. Direct Coombs test yielded negative results. Serum albumin concentration was 45 g/l and globulin 25 g/l. Serum glutamic oxalo-acetic transaminase, glutamic pyruvic transaminase, and alkaline phosphatase activities were normal. Blood tests for antibodies for toxoplasma, other viruses, rubella, cytomegalovirus, and herpes virus (TORCH) yielded negative results. An electrocardiogram (ECG) and an echocardiogram showed no abnormality. Bone marrow examination showed myeloid hyperplasia. A liver biopsy showed mild portal scarring and infiltration with chronic inflammatory cells and a skin biopsy showed hyperkeratosis and acanthosis. Antinuclear and Ro (SSA) antibodies were not detected in the blood (the specimen for the Ro (SSA) antibody was taken at 12 weeks).

**Investigations in the mother.** Her haemoglobin concentration was 8·7 g/dl. Leucocyte and platelet counts were normal and there was no evidence of haemolysis. Examination of her urine showed persistent 2+ proteinuria and microscopic haematuria. Blood tests for rheumatoid factor, antinuclear antibodies, and TORCH group of antibodies yielded negative results; Ro (SSA) antibodies were detected along with weakly positive results for reticulin and gastric parietal cell antibodies. Skin biopsy findings were consistent with a diagnosis of lupus dermatitis. Renal biopsy examination showed moderately severe proliferative glomerulonephritis, with granular deposits of IgG and $C_3$ along the capillary walls and in the mesangium.

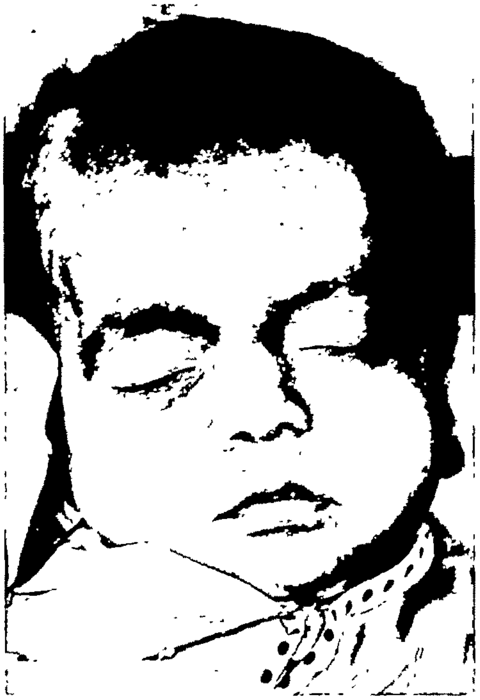

Figure *Confluent rash on the forehead and discrete lesions on the cheeks, upper lip, and chin at 5 weeks of age.*

The laboratory findings supported a diagnosis of NLE in the infant and SLE in the mother

**Hospital stay.** The baby showed evidence of continued haemolysis and he was given two blood transfusions. The rash initially increased and became confluent on the forehead but began to fade after the age of 6 weeks. At 7 weeks the boy started to have convulsions. There was generalised stiffness followed by a few jerky movements of the limbs and facial twitchings. These attacks lasted between two and five minutes and initially occurred between four and 10 times a day. Between the seizures he seemed to be well and took his feeds normally.

There was no focal neurological abnormality and he was afebrile His blood pressure, optic fundi, cerebrospinal fluid, blood glucose and urea concentrations, x-ray films of skull, EEG, computed tomogram, and urinary aminoacid chromatogram showed no abnormality. At the onset of convulsions the serum calcium concentration was 1·5 µmol/l and serum phosphorus concentration 2·6 µmol/l. Over the next few days, similarly abnormal values of serum calcium, ranging between 1·25 and 1·87 µmol/l, and phosphorus, ranging between 2·1 and 2·9 µmol/l, were found on five occasions. The baby had been exclusively breast fed

He was given calcium gluconate intravenously, which promptly controlled the convulsion. Oral supplements of calcium lactate were started. He was also given prednisolone in a dosage of 2·5 mg/day for three weeks, which was then tapered off. Convulsions recurred often during the next 10 days but thereafter decreased and stopped by 10 weeks, by which time the blood calcium and phosphorus concentrations had become normal Blood reticulocytes were 2% and the haemoglobin concentrations were stable. The baby thrived and was sent home at 16 weeks in satisfactory condition. Hepatosplenomegaly had regressed and the rash largely cleared.

## Discussion

A diagnosis of NLE in the infant and SLE in the mother was suggested by clinical and laboratory features. Although the mother's blood did not have antinuclear antibodies it was positive for Ro (SSA) antibodies. The absence of such antibodies in the blood from the baby could be due to the fact that his blood was examined fairly late in the course of the disease. Most infants with NLE are serologically negative by 6 months; in one case SSA antibodies were no longer detectable by 4 months.[2]

Interestingly, the mother had no clinical features of SLE until the eighth month of her fourth pregnancy. It is now known that most mothers of infants with NLE are asymptomatic.[1] They have an increased risk, however, of developing SLE or some other connective tissue disorder In one instance the mother of three siblings who had congenital heart block developed SLE 16 years after the birth of the first of these infants.[3]

The main features of NLE are a characteristic rash and congenital heart block, which often do not occur together.[4] Haemolytic anaemia and thrombocytopenia are seen in about 15% of cases; involvement of other systems is rare.[1] Occurrence of seizures in our patient at 7 weeks was unusual. Exclusion of other causes of convulsions by detailed investigations, including EEG and computed tomography, and the repeated finding of hypocalcaemia suggested the latter as the responsible mechanism. Such a feature has not been previously reported in NLE. Hypocalcaemia could result from transient parathyroid deficiency, possibly due to antibody mediated injury. Unfortunately, we could not examine the blood for antiparathyroid antibodies.

Siblings born after an infant with NLE may be normal or have similar or different manifestations.[1] The incidence of NLE in siblings of affected cases has been reported to be 19% [5] Although laboratory tests were not performed in the previous three siblings in the present case, all of them possibly had NLE.

NLE, caused by passive transfer of maternal antibodies, is mostly self limited, and various manifestations except heart block usually disappear by about 6 months.[2] Rarely, an infant with NLE may recover but then have SLE during adolescence.[6] NLE should be considered in the diagnosis of a neonate who has rash, heart block, and unexplained haematological abnormalities or involvement of other systems. As in the present case, NLE may lead to detection of SLE in the mother.

We are grateful to Professor A N Malaviya and Dr A E Gharavi (Rayne Institute, St Thomas's Hospital, London) for immunological investigations

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# Multiple thromboses in systemic lupus erythematosus

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SUMMARY A 5 year old girl with systemic lupus erythematosus developed extensive thromboses at multiple sites. Coagulation screen confirmed presence of the lupus anticoagulant. She recovered satisfactorily on high dose steroids without the use of anticoagulant treatment.

Patients with the lupus anticoagulant are known to have an increased tendency to develop thromboembolic complications. This has been reported only rarely, however, in young children. We report a case of extensive thrombosis in a 5 year old girl with systemic lupus erythematosus and autoimmune haemolytic anaemia.

## Case report

A 5 year old Chinese girl first presented with a history of fever and progressive pallor for one month. Clinical examination revealed striking pallor, bilateral cervical lymphadenopathy, and hepatosplenomegaly.

Laboratory investigations showed a haemoglobin concentration of 3·7 g/dl, white blood cell count $16{\cdot}9\times10^9$/l (polymorphs 79%, lymphocytes 16%, monocytes 2%, eosinophils 1%, and myelocytes 2%), platelets $105\times10^9$/l, reticulocytes 40%, and erythrocyte sedimentation rate 170 mm in the first hour. Direct Coombs test yielded strongly positive results. Rheumatoid factor and lupus erythematosus cells were negative. Serum complement (total complement CH50) was 13 units (normal 30–40 units). Antinuclear antibody and anti-deoxyribonucleic acid (anti-DNA) (double stranded) antibody (haemagglutination test 1/32) were both positive (significant at 1/4 and above). Complement binding IgG autoantibody was detected in the serum. Blood urea, electrolyte, and creatinine concentrations were normal. Urine microscopy yielded normal results.

A diagnosis of systemic lupus erythematosus with autoimmune haemolytic anaemia was made. The patient was treated with hydrocortisone and transfused with washed packed cells. She was discharged well, on treatment with oral prednisolone. After one month on a dosage of 2 mg/kg/day her blood counts were haemoglobin 12 g/dl, erythrocyte sedimentation rate 10 mm in the first hour, serum complement 33 units, and antinuclear and anti-DNA antibodies negative. A direct Coombs test yielded negative results. The steroid dosage was gradually tailed down to 5 mg every other day and she was maintained on this dose for one year. As she remained well both clinically and serologically and had no other organ involvement the steroid dosage was further tailed down and finally stopped. She was followed up closely and her blood counts and serological markers were within normal limits.

Three months after the treatment with steroids had been stopped, however, she relapsed. Her haemoglobin concentration was 8·8 g/dl, white blood cell count $8{\cdot}7\times10^9$/l, platelets $15\times10^9$/l, reticulocytes 3%, and erythrocyte sedimentation rate 130 mm in the first hour. Direct Coombs test yielded positive results. Antinuclear and anti-DNA antibodies were both negative. There was no haematuria or proteinuria to suggest any renal involvement. She was restarted on prednisolone at 2 mg/kg/day.

A week later she developed focal convulsions of left upper and lower limbs Blood pressure was systolic 100 mm Hg and diastolic 60 mm Hg. A computed tomogram of the brain showed an infarct in the right frontoparietal region. Lumbar puncture showed normal cerebrospinal fluid. She was thus diagnosed as having cerebral lupus and was pulsed with methylprednisolone 200 mg daily for three days and then continued with oral prednisolone and phenobarbitone. Three days later she developed peripheral venous thrombosis of both hands and feet. Fundoscopy of the left eye showed the retinal veins to be engorged and tortuous with multiple flame shaped retinal haemorrhages—a picture consistent with retinal vein thrombosis. Her right eye was normal. The lupus anticoagulant was detected by the method of Boey *et al*,[1] which is a modified mixing partial thromboplastin time with kaolin. The anticoagulant is considered present when a prolonged kaolin partial thromboplastin time is not corrected by the addition of normal plasma. The upper limit of normal is five seconds more than the control, above which the test is considered to be positive. This test was positive in our patient as 50:50 mixture of normal and patient's plasma was 165·2 seconds (control 70·4 seconds). Anti-thrombin 3 was assayed by both functional and immunological methods and the results were normal. The parents refused anticoagulant treatment.

Therefore she was treated only with high dose steroids and antibiotics. Fasciotomy and decompression were performed for the affected limbs. Postoperatively, all the limbs except the right hand improved. The fingers of the right hand became gangrenous (Figure). The parents refused amputation. The gangrenous fingers gradually self amputated leaving behind a stump, at the metacarpophalangeal joint. Haemoglobin concentration, platelet count, and erythrocyte sedimentation rate returned to normal and results of direct Coombs test became negative. She was discharged after four weeks of admission to hospital on phenobarbitone 30 mg twice a day and prednisolone 15 mg once a day. Treatment was tailed down gradually and she is now on alternate day prednisolone (5 mg every other day). The lupus anticoagulant factor remained positive in her serum a month after discharge. Her condition has remained stable apart from blindness of the left eye and the self amputated stump of the right hand.

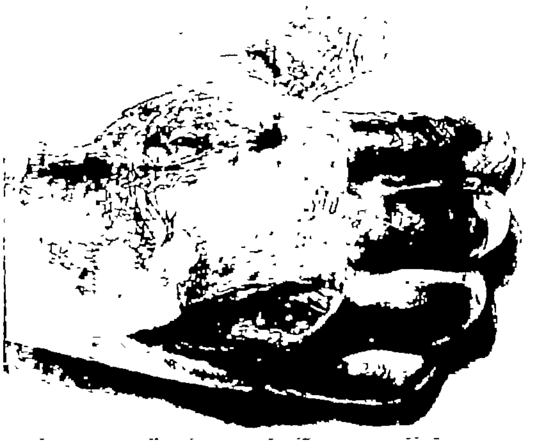

Figure *Progressive gangrene of the fingers and dorsum of the right hand despite fasciotomy and decompression.*

## Discussion

Our patient was diagnosed as having systemic lupus erythematosus at a very young age of 4 years, with autoimmune haemolytic anaemia as the presenting manifestation. A year later she developed extensive thromboses, involving the retinal veins, superficial veins of hands and feet, and most probably the cerebral veins as well, manifesting as cerebral infarction. Although thrombosis is a well recognised complication of systemic lupus erythematosus and is known to occur in renal, retinal, cerebral, pulmonary, and leg veins, it is rare for it to affect multiple sites simultaneously as it did in our patient. The coagulation screen confirmed the presence of circulating lupus anticoagulant.

The lupus anticoagulant is an acquired inhibitor of the prothrombin complex (factor XA, factor V, calcium, and phospholipid).[2] It is an immunoglobulin of either the IgG or IgM or a mixed IgG and IgM group. Carreras *et al* have shown that the gammaglobulin fraction from patients with the lupus anticoagulant inhibits production of prostacyclin by vascular endothelial cells.[3] Lower prostacyclin concentrations may result in increased platelet aggregation and thrombosis.

Patients with circulating lupus anticoagulant, paradoxically, have increased thrombotic activity, and bleeding tendency seems to be uncommon, except in cases with coexisting thrombocytopenia.[4]

Steroids, non-steroidal anti-inflammatory drugs, and cytotoxic agents have been used by others without any effect on the presence of the lupus anticoagulant.[5] Other modalities of treatment are anticoagulant treatment and plasma exchange. There have been insufficient data to conclude about the efficacy of such forms of treatment. Use of prostacyclin rather than anticoagulants in acute management is worthy of consideration. Intravenous prostacyclin has been used in severe Raynaud's phenomenon. To date there has been no report of its use in systemic lupus erythematosus with the lupus anticoagulant. Our patient responded well to treatment with steroids and has remained in a satisfactory condition on low dose steroids. She has, however, a possible long term risk of having repeated spontaneous abortions and intrauterine deaths when she reaches reproductive age.[6]

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# Swivel walkers in Duchenne muscular dystrophy

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SUMMARY Swivel walkers were used to provide low energy ambulation in 11 boys with Duchenne muscular dystrophy in schools for the physically handicapped in South Glamorgan Our preliminary experience suggests that these walkers improve the quality of life and provide a useful part of the physical treatment of the condition.

There are clear advantages in prolonging the mobilisation of boys with Duchenne muscular dystrophy, most particuarly in improving morale. The use of long leg calipers was first advocated by Spencer and Vignos in the United States[1] and has been used in the United Kingdom, particularly at the Hammersmith Hospital.[2] Nevertheless, this approach has not been universally accepted. There have been difficulties with stability, with the boys falling over easily, fitting can be complicated, and the period that the walking is prolonged can be a short one.

Swivel walkers were first introduced in America for children with amelia. The principle of their use is a pylon arrangement that uses side to side oscillation together with a forward centre of gravity to provide ambulation. Their use for children with a paraplegia was pioneered in the United Kingdom by Rose.[3] Their use for patients with muscular dystrophy was first suggested in the United Kingdom in 1981, providing a means of low energy ambulation for the boys, and has been developed by Bennett.[4] We describe our preliminary experience with swivel walkers in boys with Duchenne muscular dystrophy in schools for the physically handicapped in South Glamorgan.

## Methods and results

Most of the boys with Duchenne muscular dystrophy at the special schools for the physically handicapped in South Glamorgan (Pentwyn and Erw'r Delyn) have actively chosen to use swivel walkers as part of a programme of physical treatment for their condition. This programme has been part of a multidisciplinary, problem orientated approach to muscle disease centred at the muscle clinic and regional genetic centre at the University Hospital of Wales (Professor P Harper and Dr J R Sibert). As well as dealing with the physical problems we offer a comprehensive genetic service and active help in resolving any problems in the home situation.

In 1984 swivel walkers were introduced into the special schools and up to now have been used by 11 boys. Only one boy had declined to participate because he felt unwilling to have the extra physiotherapy involved We have used two types of swivel walkers: initially, we used the Shrewsbury type, but more recently we have had good experience with the Salford swivel walker. We have reason to believe that the Orlav swivel walker would also be satisfactory. Elective operations on the Achilles tendons have been performed in most boys to help wheelchair position and comfort and to help with the use of the swivel walkers.

The boys are placed in their swivel walkers by physiotherapists and helpers and are encouraged to walk. It takes two people about three minutes to place a boy in a walker. The boys can use their swivel walkers to go between classes or can be taken in a transporter. The distance travelled varies from 200 metres to a few metres. Our fastest patient takes about 10 minutes to travel 100 metres, but a more typical time is 20 minutes. Each boy has his own fitted swivel walker, which costs about £600. The parents are encouraged to take the apparatus home at weekends and during school holidays. All the boys who have started with these walkers are still using them, and some have had increased rather than deteriorating performance in them as measured by distance travelled and speed.

The morale of all the boys has increased using the swivel walkers. This has resulted in a greater interest in life and less depression All the parents have been pleased with this method of treatment One boy aged 16 restarted his O level course after he had abandoned it Only one boy has increased his weight centile since starting on the programme. One boy has developed scoliosis, for reasons unrelated to the swivel walker.

The mean age of the boys on beginning treatment with a wheelchair was 3·5 years and their mean intelligence quotient (IQ) was 85. All the boys managed the swivel walkers, even the three with IQs below 70. In this series the mean age of the boys while on treatment with a swivel walker was 12·4 years, with a range of 9 to 15 years. We anticipate that these figures will decrease as boys enter the programme earlier.

## Discussion

The advantage of prolonging mobilisation seems to be in preventing or reducing the inward looking attitude and depression that inevitably seems to affect boys with Duchenne muscular dystrophy. It will also help prevent obesity and may minimise deterioration in muscle power. The upright posture may also be helpful in preventing scoliosis. We have no doubt that swivel walkers are helpful to many boys with Duchenne muscular dystrophy. They do not, however, replace real walking and their use is limited to flat surfaces. They need a considerable amount of therapist time and close attention from the orthotist and the paediatrician.

Swivel walkers are difficult to fit if there are gross knee contractures and should probably be used when mobility is reduced before contractions develop. We believe that the prevention of scoliosis is important in muscular dystrophy. Scoliosis can be uncomfortable, limit upper limb function, and also be cosmetically unsatisfactory. Perhaps more importantly, it inevitably reduces lung function and probably reduces life span. We have used early jacketing to prevent scoliosis and we have been successful in all but one of our boys at special schools. The use of the Luque operation is an alternative approach to scoliosis in Duchenne muscular dystrophy.

So far we have mainly limited the use of swivel walkers to special schools for the physically handicapped in South Glamorgan. We have recently had some success with two boys, however, outside our county, one of whom attends a normal school. Both these boys have a dedicated physiotherapist and considerable parental support. Although the Warnock committee recommended that children with physical handicaps should be educated in local schools, we believe that in Duchenne muscular dystrophy there are often important advantages for boys who are educated in schools for the physically handicapped where they are able to take advantage together of a programme of physical treatment such as that outline in this paper

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# T activation haemolysis and death after blood transfusion

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SUMMARY A 30 week gestation infant developed necrotising enterocolitis associated with *Clostridium perfringens* septicaemia at 3 weeks of age. He responded to treatment with intravenous fluids, antibiotics, and blood, but his blood haemolysed. Because of anaemia further blood was given, but, within minutes he died.

Examination of his red cells showed an increase in T activation.

The T antigen is present in an occult form on all human cell surfaces. It may be shown by receptor destroying enzymes—for example, neuraminidase—which strips N-acetyl-neuraminic acid from the red cell surface, a process known as T activation This can occur during anaerobic infections, particularly those caused by clostridium species. T activation can be detected using the peanut lectin test [1] a saline extract of the peanut (*Arachis hypogea)* strongly agglutinates T activated red cells. The test can be carried out rapidly on slides at room temperature. The T antibody (anti-T) is a naturally occurring IgM antibody in adult sera, though it is not usually present in the serum of newborn infants and young children. If T activation occurs in neonates, transfusion of plasma products containing anti-T may cause or exacerbate severe or fatal haemolysis.

## Case report

The infant was the second of twins delivered by emergency lower segment caesarean section at 30 weeks' gestation for an antepartum haemorrhage due to placenta praevia. Birth weight was 1580 g. He required intensive resuscitation and developed idiopathic respiratory distress syndrome which necessitated mechanical ventilation for four days. He had an umbilical artery catheter for eight days.

By the third week of life he was making good progress and gaining weight on nasogastric feeds. There was a sudden deterioration on day 20 when he passed a bloody stool Necrotising enterocolitis was confirmed by *x*-ray and *Clostridium perfringens* was isolated from cultures of blood, stool, and skin. Haemoglobin concentration was 11·5 g/dl and spherocytosis was seen on the blood film. He was initially treated with intravenous fluids, 5% albumin solution (plasma protein fraction), antibiotics, and mechanical ventilation, and when given fresh frozen plasma and red cells in optimal additive. He had improved by the next day, but there were signs of increasing haemolysis, in 12 hours, his haemoglobin concentration fell from 12·7 g/dl to 8·8 g/dl with severe spherocytosis and his serum bilirubin concentration rose from 100 to 230 µmol/l. He developed gross haemoglobinuria. A transfusion of plasma reduced blood was started, but within minutes he collapsed and resuscitation was unsuccessful. Necropsy confirmed the diagnosis of necrotising enterocolitis affecting the colon and terminal ileum without perforation.

Repeat examination of the blood used for transfusion showed no incompatibility with the infant's

Table *Relation between clinical course and anti-T titre in blood products*

| *Day* | *Time (hrs)* | *Clinical event* | *Anti-T titre of blood product* given* | *Haemoglobin concentration (g/dl)* | *Serum bilirubin concentration (µmol/l)* | *T-Cell status** |
|---|---|---|---|---|---|---|
| 20 | 0900 | Necrotising enterocolitis diagnosed | 18 ml plasma protein fraction (O) | 11·5 | | Negative |
| | 1930 | | | 9·3 | | Weak positive |
| | 1945 | | 15 ml fresh frozen plasma (1/8) | | | |
| | | | 21 ml red cells in optimal additive (1/4) | | | |
| 21 | 0800 | Clinically improved | | 12·7 | 100 | Strong positive |
| | 2000 | Increasing haemolysis | | 8·8 | 230 | |
| 22 | 0100 | | Plasma reduced blood (1/16) | | | Strong positive |
| | 0105 | Collapse death | | | | |

†T cell status T activation of infant's red cells shown by testing with peanut lectin, *tests done by two hour incubation in tubes *v* strongly T activated cells

blood and the direct antiglobulin test (Coombs) remained negative. Using the peanut lectin test, however, increasingly strong T activation of the infant's red cells was shown The Table summarises the clinical course and shows the titre of anti-T in the various blood products used

## Discussion

Did this infant die from acute haemolysis due to T antibody in the donor blood? T activation in vivo is uncommon and usually of no clinical importance, though it interferes with blood grouping tests. It has, however rarely been associated with complement mediated haemolysis in infants, either spontaneously or through blood transfusion. Seger *et al* in 1979 stressed the potential hazards of blood and exchange transfusion in patients with necrotising enterocolitis caused by clostridia.[2] They suggested that the T antigen titre should be checked in all such cases and if positive, that the blood products be avoided. Washed red cells suspended in plasma protein fraction, should be used [3] A subsequent study reported T activation in 16 children with severe anaerobic infection, including eight with necrotising enterocolitis [4] Novak found T activation in four of 20 consecutive cases of necrotising enterocolitis, but usually associated with more extensive disease and septicaemia.[5] Severe haemolysis occurred in two infants who had previously received products containing plasma. Other authors have also described fatal haemolysis exacerbated by blood transfusion in infants with Gram negative sepsis and T activated red cells [6]

Weak T activation was detected in our patient within 12 hours of the onset of necrotising enterocolitis and clostridial septicaemia. The reaction became more strongly positive after the first blood transfusion, but clinical haemolysis did not occur until 24 hours later. Within minutes of starting the second transfusion the infant collapsed and died.

In spite of earlier reports we had previously been unaware of the potential hazards of blood transfusion in patients with necrotising enterocolitis. T activation can be detected quickly and easily with peanut lectin, and we suggest that this should be done before blood transfusion in all infants with necrotising enterocolitis or severe sepsis due to anaerobic organisms. If T activation is confirmed then blood and plasma products containing T antigen must be avoided.

We thank Dr G Mullard, Principal Scientific Officer, National Blood Transfusion Service, Lancaster, for his help

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# Annual statistical review

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It is the intention of the *Archives of Disease in Childhood* to produce an annual review of national statistics pertaining to children, and to comment on the major changes that have occurred during the year. There is a wide range of data that might be considered in this way, including those referring to demography, mortality, morbidity, behaviour and use of health and social services. This first review introduces some of these data, their source, and recent trends. We would welcome comments on areas of interest to readers.

## Demography

**Number of births.** Following a peak of just over one million births in the United Kingdom in 1964, a nadir was reached in 1977. Since then there has been a small increase and during the 1980s the annual birth rate has remained fairly stable (Fig. 1).

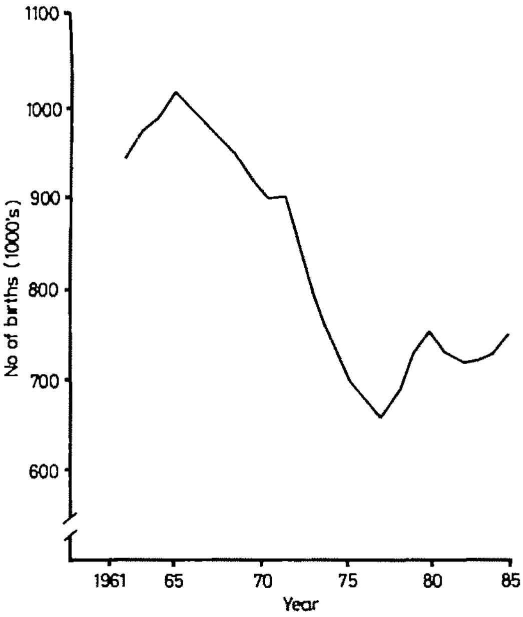


Fig. 1 *United Kingdom. trends in annual births 1961–85*

*Source Office of Population Censuses and Surveys (OPCS) Population Trends*

The number of births each year is determined by the size of the female population of childbearing age and their fertility (the general fertility rate) During the 1980s there has been a tendency to postpone pregnancy (Table 1), with a decline in fertility among women aged 20–24 and 25–29 and an increase among those aged 30 or over. These demographic shifts are relevant to such indices as perinatal and infant mortality and morbidity—for example, Down's syndrome—as these are affected by the maternal age distribution of births.

**Teenage pregnancy.** This poses problems both for the mother and the child. International comparisons of abortion, birth, and pregnancy rates (Table 2)

Table 1 *Age specific fertility rates (per 1000) in England and Wales 1980–85*

| | *Age of mother* | | | | | |
|---|---|---|---|---|---|---|
| *Year* | *<20* | *20–24* | *25–29* | *30–34* | *35–39* | *40 and over* |
| 1980 | 30 4 | 112 7 | 133 6 | 70 5 | 22 3 | 4 8 |
| 1981 | 28 1 | 105 3 | 129 1 | 68 6 | 21 7 | 4 9 |
| 1982 | 27 4 | 106 6 | 126 4 | 69 1 | 22 8 | 4 7 |
| 1983 | 26 9 | 98 5 | 126 4 | 71 5 | 23 1 | 4 8 |
| 1984 | 27 6 | 95 5 | 126 2 | 73 6 | 23 6 | 4 9 |
| 1985 | 29 5 | 94 5 | 127 6 | 76 4 | 24 1 | 5 0 |

Source OPCS Series FM1

Table 2 *Pregnancy, birth, and abortion rates per 1000 women aged 15–19 in 1981*

| | *Pregnancy* | *Birth* | *Abortion* |
|---|---|---|---|
| Netherlands | 14 3 | 9 0 | 5 3 |
| Sweden | 34 6 | 14 3 | 20 1 |
| France (1980) | 43 0 | 24 8 | 18 1 |
| England and Wales | 45 4 | 28 6 | 16 8 |
| USA | 96 0 | 52 7 | 43 3 |

Source *Report to the Ford Foundation on the finding and policy implications of a comparative study of teenage pregnancy and fertility in developed countries* New York The Alan Gutmacher Institute, 1985.

throw light on the use of family planning and abortion services by this age group. There is a wide variation in pregnancy rates from 96 per 1000 women aged 15–19 in the United States of America to 14 per 1000 in The Netherlands. Crucial to this variation is the amount of sexual activity among teenagers, for which there are no routine data. Limited evidence from special surveys, however, suggests that the proportion of teenagers indulging in sexual activity is similar throughout the Western world.[1] This being so, and assuming that spontaneous abortion rates are also similar, the differences observed in Table 2 must be attributable either to the use of contraceptives or to therapeutic abortions. American data suggest that there is a failure to practise contraception leading to high pregnancy and abortion rates. In contrast, the low pregnancy rate in the Netherlands is presumably due to widespread use of contraception England and Wales, France, and Sweden have moderate pregnancy rates.

Table 3 shows conception rates per 1000 for those aged under 16 in England and Wales between 1974 and 1984. After an initial fall these rates started rising in 1981, although recently the number terminated by abortion has increased Of concern is the pronounced increase in girls aged 14, whose conception rate rose from 4·3 per 1000 in 1980 to 5·5 in 1984.

**One parent families.** A question relevant to child health and care practices is the upward trend in one parent families. Whatever definition is used there has been a considerable increase in the number, which in a recent report,[2] was estimated as 100 000 (12%) between 1979 and 1984.

## Mortality

**Demographic effects on mortality rates.** An important innovation in the analysis of infant mortality statistics has been the routine linkage of infant death

Table 3 *Conceptions under 16 years of age in England and Wales, 1974–84*

| *Year of conception* | *Number of conceptions* | | | *Conception rates per 1000* | | |
|---|---|---|---|---|---|---|
| | *Total No of conceptions* | *Conceptions leading to births* | *Total No of terminated* | *Total No of conceptions* | *Conceptions leading to births* | *Conceptions terminated* |
| 1974 | 9371 | 4843 | 4528 | 8·5 | 4·4 | 4·1 |
| 1975 | 9181 | 4394 | 4787 | 8·1 | 3·9 | 4·2 |
| 1976 | 9191 | 4298 | 4893 | 7·9 | 3·7 | 4·2 |
| 1977 | 8993 | 4216 | 4777 | 7·6 | 3·6 | 4·0 |
| 1978 | 9103 | 4412 | 4691 | 7·6 | 3·7 | 3·9 |
| 1979 | 9108 | 4079 | 5029 | 7·5 | 3·4 | 4·2 |
| 1980 | 8580 | 3935 | 4645 | 7·2 | 3·3 | 3·9 |
| 1981 | 8561 | 3694 | 4867 | 7·3 | 3·1 | 4·2 |
| 1982 | 8999 | 3875 | 5124 | 7·8 | 3·4 | 4·4 |
| 1983 | 9369 | 4046 | 5323 | 8·3 | 3·6 | 4·7 |
| 1984 | 9649 | 4278 | 5371 | 8·6 | 3·8 | 4·8 |

Source OPCS Series FM1 No 12

Table 4 *Perinatal, neonatal, and post-neonatal mortality by maternal age, parity, and social class for England and Wales in 1984*

| | *Age of mother (legitimate births only)* | | | | | *Parity (legitimate births only)* | | | | *Social class (legitimate births only)* | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *20* | *20–24* | *25–29* | *30–34* | *35+* | *0* | *1* | *2* | *3+* | *I* | *II* | *III NM* | *III M* | *IV* | *V* | *Others* |
| *Perinatal mortality | 13·6 | 10·0 | 9·1 | 9·0 | 13·3 | 10·4 | 7·8 | 9·3 | 13·5 | 7·1 | 7·9 | 8·2 | 9·8 | 11·6 | 14·1 | 9·8 |
| †Neonatal mortality | 7·8 | 5·5 | 5·1 | 4·8 | 6·4 | 5·6 | 4·7 | 5·1 | 6·8 | 4·1 | 4·5 | 4·5 | 5·6 | 6·3 | 7·2 | 5·6 |
| †Post-neonatal mortality | 6·5 | 4·8 | 3·0 | 3·1 | 2·8 | 2·5 | 3·7 | 4·2 | 4·8 | 2·2 | 2·6 | 3·1 | 3·2 | 4·0 | 5·7 | 6·7 |

Source OPCS Series DH3 No 17
*Per 1000 total births, †per 1000 live births

and birth registration documents for England and Wales Throughout the 1980s linkage has been successfully achieved for over 98% of infant deaths, which permitted the analysis of perinatal and infant mortality rates by mother's age, parity, and social class (Table 4). These data have directed attention to the importance of social factors and patterns of child bearing on mortality risk. Unfortunately, up to date figures on childhood mortality risk by social class are not yet available, having been excluded from the most recent *Decennial Supplement on Occupational Mortality* [3] We know, however, from previous reports that the gradient of risk with social class is even sharper in childhood than in infancy, particularly for accidental deaths.

**Perinatal mortality.** In 1965 The World Health Organisation recommended that the perinatal period should include all deaths after the twenty-eighth completed week of gestation and early neonatal deaths of seven days or less. This definition still stands, but largely as a result of neonatal intensive and special care, there have been suggestions that the period should be extended from after the twentieth completed week of gestation to the end of the neonatal period (28 days). Perinatal mortality in the United Kingdom in 1985, for the first time, was in single figures at 9·9 per 1000 total births.

**Neonatal mortality.** The division of infancy into neonatal and post-neonatal periods was suggested over a century ago by William Farr because the causes of death in the two periods were so different and influenced by such different factors. In developing countries post-neonatal deaths comprise the largest proportion of infant deaths; in developed countries the reverse applies, and it is more appropriate to examine neonatal and post-neonatal mortality separately.

Table 5 shows the trends in the causes of death in the neonatal period. The pattern is dominated by two groups according to the *International Classification of Diseases* (ICD)—congenital anomalies and certain conditions originating in the perinatal period. In the latter group, retardation of fetal growth and immaturity and hypoxia and birth asphyxia are the main causes of death

The decline in neonatal mortality due to congenital anomalies is partly due to the striking fall in the prevalence of neural tube defects (Fig. 2). The downward trend began in about 1974 and was still evident in 1985 but can be attributed only in part to the programme of screening for neural tube defects. The cost effectiveness of this programme is decreasing as the birth prevalence declines.

**Post-neonatal mortality.** While perinatal and neonatal mortalities have shown a progressive and in recent years accelerated reduction, post-neonatal mortality has only marginally improved (Fig. 3). Table 6 shows comparisons of international post-neonatal mortality. In most Western countries the rate has not changed much over the past decade, though different countries are stabilising at different levels. Because the numbers of post-neonatal deaths in some countries are now so few, random variation accounts for much of the annual fluctuation.

The causes of death in the post-neonatal period differ from those in the neonatal period (Tables 5

Table 5 *Neonatal deaths by cause for England and Wales in 1984 (rates per 1000 live births)*

| | *1980* | *1981* | *1982* | *1983* | *1984* |
|---|---|---|---|---|---|
| Diseases of the respiratory system (ICD 460–519) | 0·18 | 0·17 | 0·14 | 0·15 | 0·10 |
| Congenital anomalies (ICD 740–759) | 2·36 | 2·12 | 2·05 | 1·84 | 1·76 |
| Certain conditions originating in the perinatal period (ICD 760–779) | 4·59 | 3·98 | 3·73 | 3·58 | 3·35 |
| All causes | 7·60 | 6·66 | 6·27 | 5·85 | 5·57 |

Source OPCS Series DH3

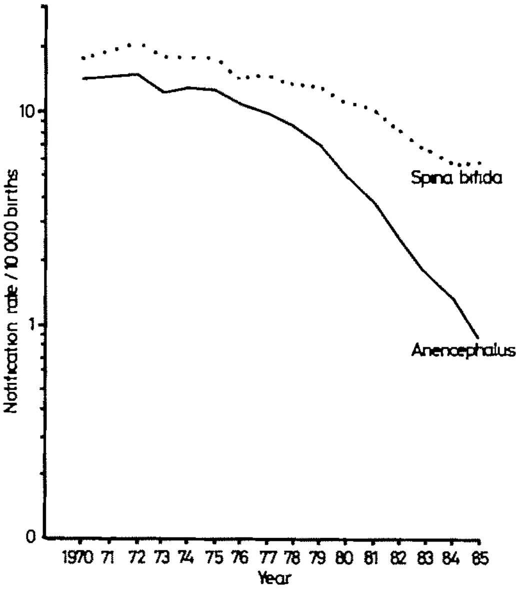
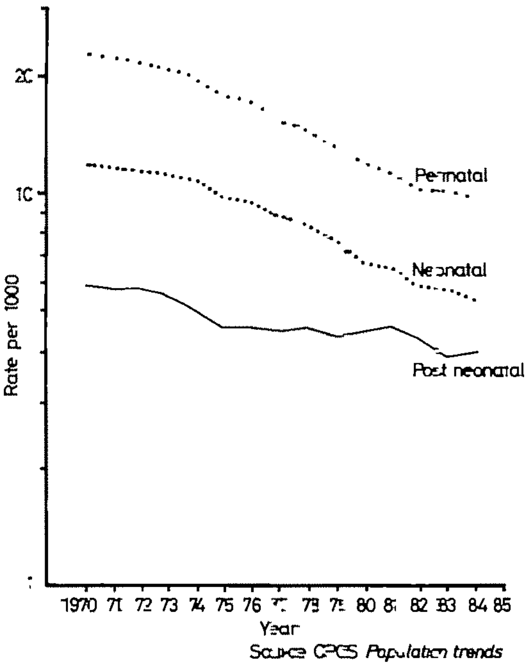


Fig. 2 *Neural tube defect notification rates.*

*Source OPCS Monitor MB3 86/2*



Source OPCS Population trends

Fig. 3 Infant mortality (United Kingdom).

Table 6 *International comparisons of post-neonatal mortality (rates per 1000 live births)*

| | *1980* | *1981* | *1982* | *1983* | *1984* | *1985* |
|---|---|---|---|---|---|---|
| Denmark | 2.9 | 2.9 | 3– | 3.1 | NA | NA |
| England and Wales | 4.3 | 4.4 | 4– | 4.2 | 3.9 | 4.0 |
| Germany | 4.8 | NA | NA | 4.5 | 4.4 | NA |
| Netherlands | 2.9 | 2.9 | 3– | 3.1 | NA | NA |
| Scotland | 4.3 | 4.4 | 4– | 4.3 | 4.1 | 3.9 |
| United States | 4.1 | 3.9 | 3– | 3.3 | 3.8 | NA |

Source WHO annual statistics, OPCS Population trends
NA=not available

Table 7 *Post-neonatal deaths by cause (rates per 1000 live births)*

| | *1980* | *1981* | *1982* | *1983* | *1984* |
|---|---|---|---|---|---|
| Infectious and parasitic diseases (ICD 000–134) | 0.16 | 0.17 | 0.13 | 0.14 | 0.12 |
| Diseases of the respiratory system (ICD 460–519) | 1.03 | 0.88 | 0.88 | 0.71 | 0.55 |
| Congenital anomalies (ICD 740–759) | 0.77 | 0.90 | 0.93 | 0.86 | 0.82 |
| Sudden death, cause unknown (ICD 798) | 1.42 | 1.55 | 1.73 | 1.65 | 1.60 |
| All causes | 4.46 | 4.41 | 4.55 | 4.29 | 3.91 |

Source: OPCS Series DH3

and 7). As a specific category 'sudden death, cause unknown' first began to be registered in large numbers about 1970 after which it rapidly peaked in 1982; it now accounts for about 40% of post-neonatal deaths. During this period there has been little change in the rate for the combined categories, 'diseases of the respiratory system' and 'sudden death, cause unknown', which is probably due to the changing pattern of certification; most deaths now recognised as sudden infant deaths would formerly have been registed as respiratory conditions.

**Childhood mortality.** Fig. 4 shows recent trends in early and childhood mortality Although overall trends for all ages are fairly consistently downward, certain features cause concern, the flattening out of mortality in the 10–14 year age group; and the number of deaths due to accidents.

**Mortality directly related to birth weight.** National data on birth weight arising from the birth notification system have been available since 1953 for live births and 1955 for stillbirths Until 1975 data on birth weight were only for births of 2500 g or less and this has proved a serious deficiency. For infants of normal birth weight (over 2500 g) it is necessary to subtract the low birthweight notifications from total birth registrations. As these data sets arise from different sources discrepancies occur; it is also impossible to divide the bigger infants into birthweight subgroups. A further problem lies in the class intervals used. The birthweight groups tabulated are <1000 g, 1001–1500 g, 1501–2000 g, 2001–2250 g, and 2251–2500 g, which differ from the WHO groups of up to 999 g, 1000–1499 g, 1500–1999 g etc. Because of the tendency to record birth weight to the nearest 10 g, important differences may arise between the two systems, particularly among the very low birthweight infants.

In 1975 the Office of Population Censuses and Surveys (OPCS) in association with local health authorities and the birth notification system first started recording birth weight as part of the registration procedure. Initially the birth weight was registered in only 50–60% of infants but by 1984 this had improved to almost 100% of live births and in over 98% of stillbirths. Table 8 shows birthweight specific stillbirths and infant mortality for 1984. It is noticeable that these rates are high in those infants whose birth weight was not registered. This group is probably biased by the inclusion of an excess of low birthweight infants who die soon after birth but before they have been weighed. Some of these infants were not weighed because they were considered to be too ill; it is increasingly being recognised, however, that proper clinical manage-

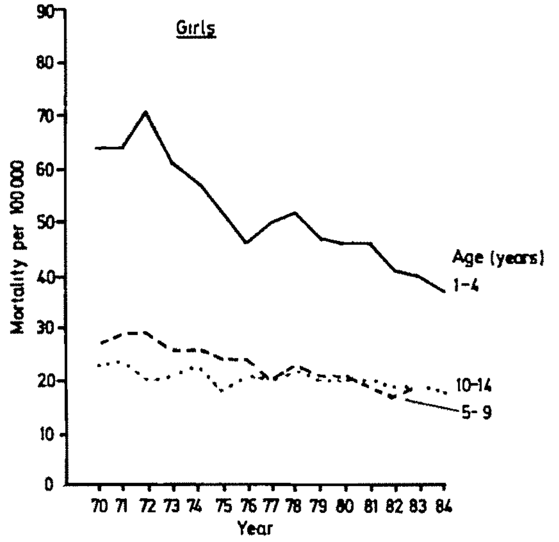
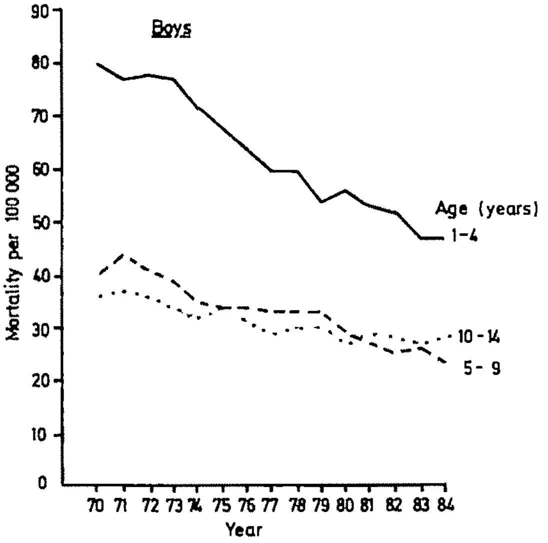


Fig 4 Childhood mortality for females in England and Wales



Childhood mortality for males in England and Wales

Source OPCS Series DH1

ment of these babies cannot be adequate if their weight is not known so that in future this category of 'not weighed' should decrease.

International comparisons of birthweight specific mortality are difficult for several reasons. In spite of birth weight having a major influence on mortality, few of even the developed nations provide birthweight specific data When data are available, the birthweight class intervals may not coincide and mortality may not refer to the same periods in infancy. Table 9 shows perinatal and neonatal birthweight specific rates for England and Wales and Denmark (1983) and for Sweden (perinatal only) (1981). These figures should not, however, be taken at face value, there may be differences in the registration of infants of very low birth weight and gestational age less than 28 weeks, and also in the proportion of births for which birth weight was not stated. As the latter are predominantly infants of low birth weight, there will be a corresponding bias in mortality

**Notifiable diseases.** The OPCS annually produces data on the number of cases of notifiable diseases. Fig. 5 shows examples of the trends in notification of whooping cough and measles.

Data on vaccination rates are published in the Department of Health and Social Security (DHSS) annual report, the *State of the Public Health.* Table 10 shows trends in the vaccination rates since 1974 The pronounced lowering of the vaccination rates for whooping cough following the adverse publicity given to the vaccine in 1976 is clearly evident. There were smaller effects on vaccination rates for diphtheria, tetanus, and poliomyelitis. The rate of vaccination for pertussis is slowly increasing again,

Table 8 *Birthweight specific mortality for England and Wales in 1984*

| *Mortality* | *Birth weight* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *<1500 g* | *1500–1999 g* | *2000–2499 g* | *2500–2999 g* | *3000–3499 g* | *3500–3999 g* | *4000 and over* | *Not stated* |
| *Stillbirth | 165 4 | 61 3 | 20 7 | 4 8 | 1 7 | 1 3 | 1 9 | 77 3 |
| *Perinatal | 365 9 | 94 7 | 30 4 | 7 3 | 2 8 | 2 1 | 2 8 | 242 0 |
| †Neonatal | 278 9 | 44 3 | 12 0 | 3 6 | 1 7 | 1 1 | 1 2 | 204 8 |
| †Post-neonatal | 36 6 | 16 6 | 8 7 | 4 7 | 3 0 | 2 4 | 1 7 | 16 0 |
| †Infant | 315 4 | 60 9 | 20 0 | 8 3 | 4 7 | 3 6 | 3 0 | 220 4 |

Source OPCS Monitor DH3 86/1
*Per 1000 total births, †per 1000 live births

Table 9 *International comparisons of birthweight specific mortality*

| Birth weight (g) | Perinatal mortality (rates per 1000 total births) | | | Neonatal mortality (rates per 1000 livebirths) | |
|---|---|---|---|---|---|
| | England and Wales* | Denmark* | Sweden† | England and Wales* | Denmark* |
| –1499 | 387 6 | 330 5 | 339 1 | 295 5 | 266 2 |
| 1500–1999 | 103 3 | 117 4 | 90 1 | 46 6 | 43 1 |
| 2000–2499 | 30 2 | 27 6 | 34 1 | 13 3 | 8 1 |
| 2500–2999 | 7 5 | 8 3 | 9 4 | 3 7 | 3 5 |
| 3000–3499 | 2 8 | 2 9 | 2 4 | 1 7 | 1 3 |
| 3500–3999 | 2 2 | 2 3 | 1 9 | 1 4 | 1·0 |
| 4000 and over | 2·8 | 2 6 | 1 6 | 1 5 | 1 6 |
| Not stated | 227·7 | 130 4 | 245 8 | 205 8 | 130 4 |

*1983, †1981: Source OPCS Monitor DH3 35/1, Medicinsk fodelseregistrering 1983 (Denmark), Medicinsk fodelseregistrering 1981 (Sweden)

as is that for measles, which has been a more recent addition to the vaccination programme

**Other morbidity indicators.** Every year the results of a sample survey of households (*General Household Survey*) is published showing tables on long standing and limited illness, hospital outpatient attendance in a three month period, general practitioner consultations in the 14 days before the interview, and average number of consultations each year. Data from these surveys show an apparent rise in self-reporting of longstanding illness, and in use of general practitioner services, over the 10 years from 1974–83. The reporting of illness in members of any household is to some extent related to expectation and views of health, and it is likely that the observed rise reflects these aspects rather than changes in incidence of disease. Data on trends in hospital discharges for children can be obtained from the Hospital In-Patient Enquiry (Table 11). There has been a slight increase recently in all three age groups shown, but the pattern is not consistent. Regular surveys are also carried out on dental health[4] and smoking habits in childhood,[5] and these form an important part of our knowledge of child health. These statistics are difficult to interpret because of the frequent changes of age grouping; we hope this will be corrected in future. There is also a striking lack of national data on trends in childhood growth.[6]

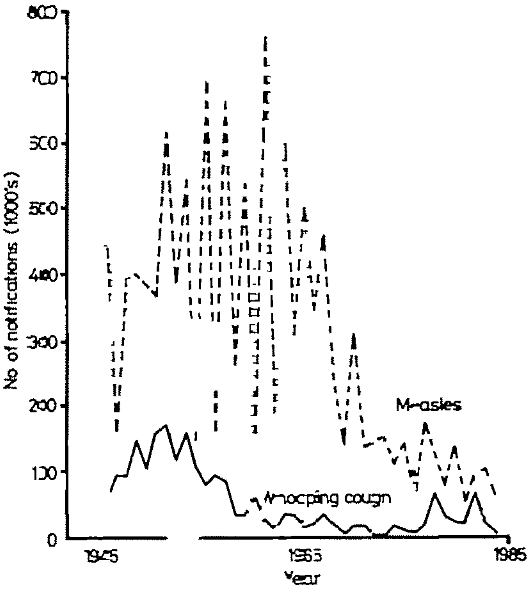


Fig. 5 *Measles and whooping cough notifications.*

*Source OPCS Series MB2 Registrar General's Statistical Review of England and Wales Part 1*

**Personal Social Services Statistics.** Another aspect of trends in child health can be seen in data on the use

Table 10 *Trends in vaccination rates percentage of children vaccinated before 3 years of age (England)*

| | *Diphtheria* | *Whooping cough* | *Tetanus* | *Polio-myelitis* | *Measles* |
|---|---|---|---|---|---|
| 1974 | 83 | 80 | 83 | 82 | 56 |
| 1975 | 81 | 78 | 82 | 81 | 55 |
| 1976 | 77 | 61 | 77 | 77 | 50 |
| 1977 | 78 | 39 | 78 | 77 | 51 |
| 1978 | 80 | 41 | 80 | 80 | 52 |
| 1979 | 81 | 31 | 81 | 81 | 51 |
| 1980 | 82 | 35 | 82 | 82 | 54 |
| 1981 | 83 | 42 | 83 | 83 | 55 |
| 1982 | 85 | 47 | 85 | 84 | 57 |
| 1983 | 86 | 55 | 86 | 86 | 61 |
| 1984 | 86 | 60 | 86 | 85 | 63 |

Source DHSS On the State of the Public Health (Annual Reports) of personal social services. Table 12 shows the numbers of children who are in the care of local authorities; data on nursery services and registered child minders are also available. Benefits related to childbearing are difficult to obtain from a single source; some indication, however, of the effect of children on the financial status of the family is shown in Fig. 6. A married couple with four dependent children, despite an increase in earnings from £60 to £135, would have an unchanged net spending power of about £110 because of the increase in income tax and withdrawal of means tested benefits.

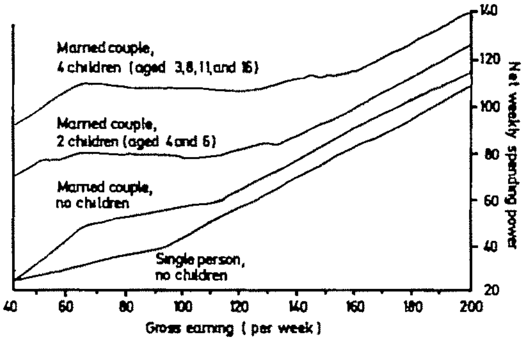


Fig. 6 *Net weekly spending power by level of gross earnings and type of family (April 1985)*

*Source Central Statistical Office Social Trends 1986*

## Summary

We have given an indication of the range of national data which are available on child health. Paediatricians are familiar with simple demographic, mortality, and morbidity statistics, and it is intended that trends in these should be updated annually. There is, however, a wealth of data on the use of medical social, and financial services which will be reported in future. Professional interest may help to improve the collection and presentation of national data, and we hope that this series will do this as well as providing a source of data for those who do not otherwise have access to it.

Table 11 *Trends in hospital discharge rates per 10 000 population in England 1979–84*

| *Age group (years)* | *1979* | *1980* | *1981* | *1982* | *1983* | *1984* |
|---|---|---|---|---|---|---|
| 0–4 | 1309 | 1334 | 1378 | 1406 | 1403 | 1427 |
| 5–9 | 650 | 685 | 702 | 682 | 717 | 716 |
| 10–14 | 467 | 491 | 501 | 501 | 523 | 535 |

Source OPCS Monitor MB4 86/1.

Table 12 *No (000's) of children in care of local authorities in England*

| *Age (years)* | *1973* | *1979* | *1980* | *1981* | *1982* | *1983* |
|---|---|---|---|---|---|---|
| <5 | 12 0 | 9 9 | 10 1 | 9 6 | 9 6 | 8 7 |
| 5–15 | 56 6 | 61 7 | 62 1 | 59 9 | 56 5 | 51 8 |
| 16 and over | 20·3 | 23 6 | 23 0 | 22 7 | 22 6 | 21 7 |
| All children | 88·8 | 95 2 | 95 3 | 92 3 | 88 7 | 82 2 |

Source DHSS, Health and Personal Social Services Statistics for England 1985

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## *Personal practice*

# Guidance for divorcing parents

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Divorce is endemic in the Western world; in Britain one marriage in three ends in divorce, and in the United States the proportion is one in two. When their parents are divorced children are exposed to special dangers to their psychological development. The family is the main source of psychosocial elements essential for healthy development—love, nurture, control, and guidance—and is the environment in which personality and gender are moulded. Its breakdown, in depriving children of these, represents major stress. At the same time the parents' preoccupation with their conjugal struggles interferes with their ability to support their children in coming to terms with this and other stresses without psychological or social maladjustment. Most children show signs of their stress through anxiety, anger, irritability, depression, bodily complaints, and deterioration in academic performance during the year after divorce. About 30–40% suffer subsequently from enduring psychopathology or social maladjustment such as depression, aggressiveness, and lack of self discipline that leads to delinquency, promiscuity, alcoholism, or drug addiction. This proportion is two or three times more than the proportion that would be expected in children whose parents were in serious conflict but did not divorce.

Paediatricians who wish to reduce current suffering and future incapacity may seek to lower the intensity of the stress caused to children and help parents devote special effort to supporting their children in mastering this stress. A list follows of guidelines for paediatricians who wish to help their patients by educating their parents.

Parents intending to divorce should discuss the issues with their children before the separation to prepare them for what is about to happen in a manner geared to their ages and developmental levels. With preschool children this discussion should take place a week or two before the family's break up; with 5–8 year olds the discussion should be a month or two beforehand; older children should be given longer notice. If possible parents should talk to their children together to show that they agree. They should expect that, after this first discussion, they will need to continue talking about the issues with the children as a group or individually depending on the children's reactions and the questions they raise. The initial discussion should cover the following 10 points.

(1) The parents intend to end their marriage, live in separate homes, and no longer be husband and wife because they have stopped loving each other and cannot live peacefully with each other; the divorce has not been caused by anything the children have done.

(2) The couple intend to continue as parents of their children, to love them and care for them throughout childhood. They promise this without regard to what may happen in the future, when one or other may remarry and have additional children.

(3) The children will live in the home of one parent and visit the other parent regularly. The parents know that children need continuing contact with both of them for healthy growth and development, and both want the children to maintain close links with each parent

(4) The divorce will be permanent. If the parents stop quarrelling after the separation and become friendly as they once used to be this does not mean that they will live together again.

(5) The parents realise that the children will probably oppose the divorce because it breaks up their home, but the children cannot alter their decision and should not try to do so. It has been made by the adults because of adult problems.

(6) The parents know that the children may feel angry, upset, and insecure. They have taken these reactions into account and are sorry about them. They will help the children master these feelings; most children succeed in this over a few months.

(7) Divorce is common; every second or third marriage ends in this way. Thus the children should not feel different from others; they should not feel

ashamed because their parents have divorced. Like other family matters this is private, but the children should feel free to talk about it to their close friends and their teachers. It often helps to share such matters with others who can provide support in times of difficulty. If, for a few weeks, thoughts about family troubles interfere with the children's capacity to concentrate in the classroom or in homework it would be good for their teachers to know what is happening and help the children overcome the temporary difficulties.

(8) The children should stay out of the quarrels between the parents, they should definitely not take sides Even though the parents have stopped loving each other they continue to love their children and will always do so. They each want the children to love the other parent. They will do their best not to say bad things about each other to the children; if because of anger they do not always succeed, the children should forgive them

(9) The parents do not wish the children to carry messages from one to the other, and promise to try not to send messages through the children. They do not wish the children to tell them what the other parent has been doing

(10) The parents jointly or individually will talk to the children about these matters from time to time before and after the divorce. They know that it will be hard for the children to understand and come to terms with what is happening and that it will take a long time for them to adjust to the division of their family into two separate homes The children should express their feelings in any way that is comfortable and should feel free to ask questions, which the parents will try to answer

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## *Current topic*

# Vaccination and cot deaths in perspective

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SUMMARY In 1985 twin boys simultaneously succumbed to sudden unexpected deaths two to three hours after vaccination with diphtheria, tetanus, and pertussis vaccine (DTP). This occurrence again raises the question of whether an association of sudden infant death (SID) with vaccination is other than temporal. Taking the incidence of SID in conjunction with rates of infant vaccination in the United Kingdom, nine infants would be expected to die, each year by chance alone, suddenly within 24 hours of (and within each 24 hour period succeeding) vaccination with DTP. Twins are at a greater risk of SID than single born infants and occasionally are found dead together. A number of studies into DTP vaccination as a risk factor in SID have shown that SID is less common in vaccinated than in unvaccinated infants.

Sudden infant death (SID) is a term used for those unexpected sudden deaths of infants that cannot be adequately explained and is often characterised by the baby being found dead in its cot. It has a characteristic age distribution, occurring chiefly in infants less than 1 year old and peaking in those aged 2–3 months. Theories abound about the possible causes, and vaccination has been put forward as one of these, chiefly because of occasional temporal association. The simultaneous deaths of 5 month old twin boys within three hours of vaccination with adsorbed diphtheria, tetanus, and pertussis vaccine (DTP) again raises the question of association with vaccination.

### Incidences of SID

Golding *et al* surveyed the epidemiological studies of SID and derived the following incidence figures.[1] Fourteen studies in North America showed an incidence of SID of 2-3 per 1000 live births. In Sweden the incidence was lower, with 1 per 1000 live births. In the United Kingdom the mean (SD) incidence across eight surveys was 2 (0·62) per 1000.[1] Variations between studies can be accounted for partly by real differences. there are certainly fewer cases of SID in Sweden where infant mortality due to all causes is very low. Artefactual variations arise from two sources. Different studies include SID from different age groups, by excluding perinatal mortality within variable periods up to 1 month of age, and by excluding children older than 1 or 2 years. A more serious source of variation is in diagnosis. Since 1972 the term 'sudden infant death' has been accepted by coroners as an explanation for infant deaths on certificates. Its use is variable, and in recent years it has taken the place of respiratory causes on death certificates. Thus in some studies SID is taken to include deaths that would not be included in other studies.

### Probability of SID coincident with DTP vaccination

Fedrick's Oxford record linkage survey was a large survey of 206 cases of SID that occurred over five years at an incidence of 2·78 per 1000 live births.[2] The distribution of cases of SID in different age groups was broken down· 88% were in the first year of life and 30% between 3 and 6 months. Thus the incidence during the first year was 88% of 2·78/1000—that is, 2·45/1000—and between 3 and 6 months was 30% of 2·78/1000—that is, 0·83/1000. These figures can be used for the following observations, where:

D=Number of days in age band—for example, 365 in one year, 91 in 3–6 months.

Pc=Probability of SID in a child in a specified age band. This is equal to the incidence of SID in that age band.

Pd=Average daily probability of SID in a child in a specified age band.

I=Total number of DTP inoculations administered to children in an age band per year. No child receives more than one per day.

N=Expected number of children per year, in specified age band, to suffer SID within 24 hours of DTP vaccination.

So (i) $Pd=\frac{Po}{D}$ and

(ii) $N=Pd\times I$.

From (i), the average daily probability (Pd) of SID in a child during its first year=$(2{\cdot}45/1000)\div365=6{\cdot}7\times10^{-6}$; also the average daily probability of SID in a child between the ages of 3 and 6 months=$(0{\cdot}83/1000)-91=9{\cdot}1\times10^{-6}$.

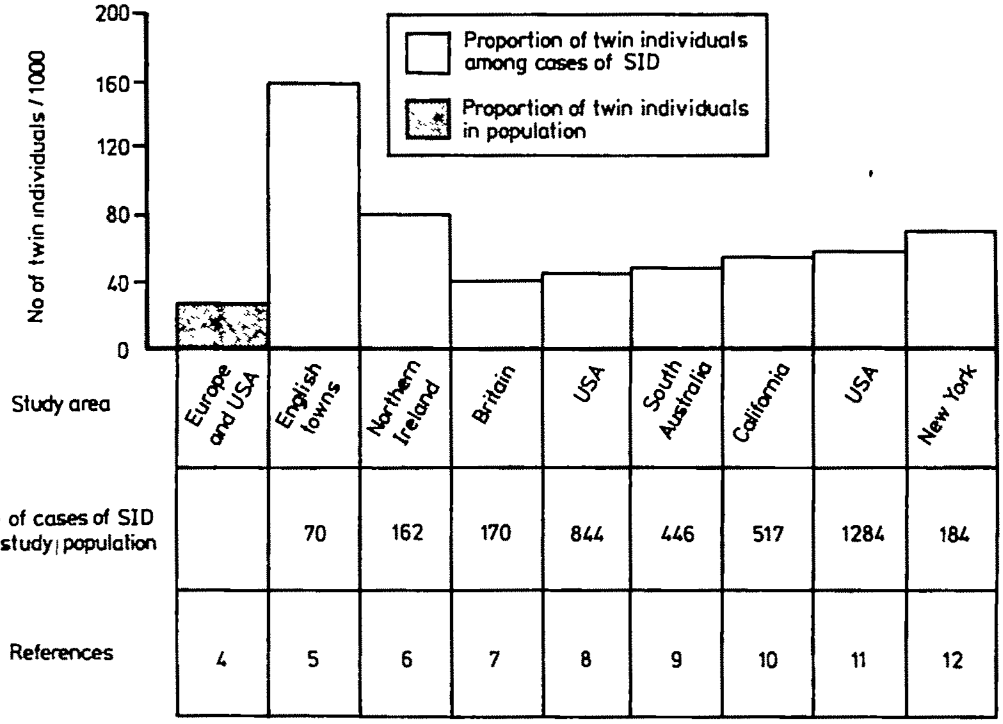
In the United Kingdom there are 700 000 live births a year[3] and DTP vaccination is taken up for roughly 66% of infants—that is, for 460 000. Each infant receives a course of three doses of vaccine, beginning between 3 and 6 months, with the second dose following after 6–8 weeks and the third dose given 4–6 months later To simplify the calculations it will be assumed that all 1·4 million doses of DTP (460 000×3) are given each year to infants in their first year, with 930 000 doses (the first and second vaccinations) being given to children aged 3–6 months.

From (ii), the number per year (N) likely to die suddenly within 24 hours of vaccination with DTP=$(6{\cdot}7\times10^{-6})\times1\,400\,000=9{\cdot}4$. Similarly, the number likely to die suddenly within 24 hours of vaccination with the first or second dose of DTP=$(9{\cdot}1\times10^{-6})\times930\,000=8{\cdot}5$.

As described, neither the risk of SID nor the probability of being vaccinated are evenly distributed throughout the first year of life. Ideally, the daily risk of either event occurring could be calculated and precise probabilities of concurrence obtained. The calculations have been kept simple to allow easy adaptation to any population. The estimates are likely to be inflated for two reasons:

1. (1) Some infants that die unexpectedly have symptoms for some days and therefore may not have been vaccinated.
2. (2) SID is associated with poor uptake of health services and hence with undervaccination.

The number of deaths reported as adverse reactions does not approach the expected level. Wellcome, who for several years have been the sole



| Study area | Europe and USA | English towns | Northern Ireland | Britain | USA | South Australia | California | USA | New York |
|---|---|---|---|---|---|---|---|---|---|
| No of cases of SID in study population | | 70 | 162 | 170 | 844 | 446 | 517 | 1284 | 184 |
| References | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |

Fig 1 *Proportion of twin born children among cases of sudden infant death (SID) from eight studies (white bars). Normal proportion of twin born individuals in live born population is shown as the black bar.*

manufacturers of DTP vaccine in the United Kingdom, have received reports through the committee on the safety of medicines of six cot deaths occurring after DTP vaccination in over 20 years of reporting, but there were probably additional cases that were not reported. During the 14 months after the widely publicised case of the twins a further five cot deaths have been reported to Wellcome as occurring within 24 hours of vaccination in the United Kingdom.

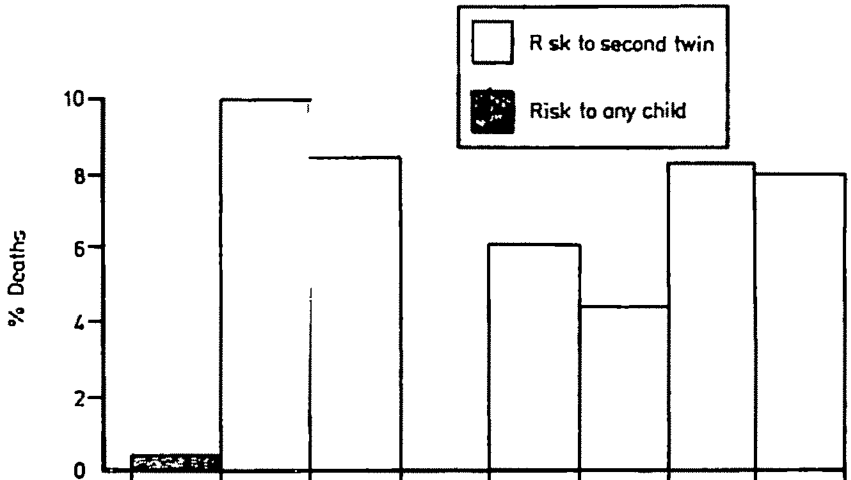
## Risk of SID in twins

The chance of two independent children dying simultaneously after vaccination is remote, but it is interesting to note some special features of the risk of SID to twins.

An average of 12 in every 1000 live births in Europe and North America are twins[4]—that is, 24 twin individuals. The number of twins found among SID victims is out of proportion to their representation in the population. This has been found in several studies of SID (Fig. 1), with about a threefold higher proportion of twins among cases of SID. In three of these studies, of 170, 184, and 162 cases of SID, respectively, the authors additionally compared the risk of SID in twins with that in specific control populations.[7 12 6] Knowelden *et al* selected 151 age matched controls from the population and found a fourfold higher proportion of twins among cases of SID [7] Standfast *et al* compared death rates among single born children (singletons) with those among twins and found the risk of dying of SID for twins was 3·9 times higher than for singletons.[12] Froggatt *et al* compared SID with deaths by other causes and found an especially high risk of SID to twins, with twins constituting 8% of SIDs and 3·5% of other deaths [6]

## Concordant SID in twins

Of particular note is the greatly increased risk to the second twin if the first twin dies. This is illustrated in



| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| No of twin pairs with one or more cases of SID | | 10 | 12 | 37 | 17 | 66 | 207 | 25 |
| No of concordant twin deaths | | 1 | 1 | 0 | 1 | 3 | 17 | 2 |
| No of coeval concordant cases of SID | | 1 | 1 | 0 | 1 | 0 | 9 | 1 |
| References | 1 | 5 | 6 | 8 | 9 | 11 | 13 | 10 and 14 |

Fig. 2 *Risk of sudden infant death (SID) to a twin of a SID victim, showing the number of twins per 100 that succumb, given that their twins have died The black control bar shows the normal risk to any child (at 2·5 per 1000)*

Figure 2. The black bar shows a normal rate of cases of SID in the population at around 0·25%.[1] The risk to the second twin in six studies was between 5 and 10%, although one study found no deaths in second twins.[8] It is not uncommon for such concordant deaths to be coeval—that is, to occur on the same day—often with the twins being found dead together. Three concordant deaths described in three separate studies were all coeval.[5 6 9] Cooke and Welch additionally described three cases of concordant, coeval SID in twins that they studied in nearby towns (not part of their study population)[5] Spiers' study was specifically of twins.[13] The number of cases of SID he describes is inflated because he excluded only deaths ascribed to traumatic causes. Only his home deaths figures are reported here, since the hospital deaths were less likely to be cases of SID. Half of the concordant deaths that he studied were coeval.

Smialek identified and presented reports on nine cases of coeval concordant twin deaths in the United States and Europe, occurring between 1966 and 1981.[15] In a study of 112 cases of SID occurring in twins over four years in England and Wales Carpenter described two coeval concordant twin deaths and estimated the rate of SID in twins to be 2·2/1000, compared with a rate of 1·4/1000 in the general population[16]

The increased risk to the second twin does not argue a genetic explanation for SID; rather, simultaneous twin deaths seem to be because of shared environment (which could include exposure to pathogenic organisms). Thus no difference in risk has been found between identical and non-identical twins.[11 13] Data indicating that subsequent (non-twin) siblings of SID victims were at high risk of SID themselves have been refuted and updated by Peterson *et al*[17] with data from Washington that concur with the results of a Norwegian study.[18] The latter found a rate of SID of 0·48% in subsequent siblings, compared with 0·13% in the population· in Washington the rate was 0·74%, not significantly different from the 0·4% rate found in controls.

A study of 12 families with two or more cot deaths implicated psychosocial factors as the chief cause of repeated cases of SID within the family.[19] In another study investigations at the scene of death of 26 cases of SID recorded that in at least six cases accidental death was implicated and that in almost all cases the situation was exacerbated by poor judgment by the caretaker of the infant.[20] Of these 26 infants, four were members of a twin pair, and one was a triplet.

One factor that puts twins at higher risk is their low birth weights, a known predisposing factor for SID in infants.[21] In a study of 42 twin pairs in which one twin had died Kahn *et al* found both the weights and heights at birth of the SID victim to be significantly lower than those of the surviving twin and of 42 control twins[22]

The twins who died in 1985 were not identical This makes an idiosyncratic response to the vaccine unlikely That they should have died together was an extraordinary event but, as shown above, not without precedent from reported cases. A case of identical twins both dying, 16 and 20 hours after vaccination with diphtheria toxoid and pertussis antigen, was reported in 1946[23] and was attributed to delayed anaphylactic shock.

## DTP vaccination as a risk factor for SID

DTP vaccination is now often examined as a risk factor in epidemiological studies of SID after reports of clusters of cases of SID after vaccination in Tennessee and Oslo.[24–26] The Oslo cluster was studied in relation to a larger area of Norway and found to be non-significant[26] The authors of this study suggested that the cluster in Tennessee was real and was an example of the 5% of occasions in which associations will be found, by chance, to be significant Two interesting points come out of these studies of clusters· firstly, once a 'scare' has begun adverse reaction reporting multiplies through increased awareness, secondly, looking for associations in many places and at many times will certainly reveal sporadic associations that need not be causal In the Oslo cluster deaths occurred one week and in Tennessee one day after vaccination.

DTP vaccination seemed to be further implicated by a paper that purported to show an excess of cases of SID close to the time of vaccination among 27 such deaths occurring within a month of vaccination[27] This paper has been criticised on account of methodological flaws, such as an inadequate control group.[28] The survey was retrospective and so recall bias might be expected.[29] The dependence of the study on telephone contact of parents, for lack of which 80% of the original study population of 382 SID victims was dropped from the study, would have introduced a socioeconomic bias. The multiple testing using different periods is statistically unacceptable and Mortimer *et al's* retesting with a 2×7 contingency table showed no significant difference in distribution of deaths between the vaccinated and 'control' populations.[29]

In other studies that have looked at vaccination and SID there have been fewer vaccinated infants among SID victims than among control infants Thus in a study of 146 deaths in infants that died with no known predisposing organic disease, of which 47 were defined as SID, the rate of vaccination of any kind was 13%, compared with an approximate 60% uptake in the population at large.[30] A study of 26 unexpected infant deaths, each with two age matched controls, found the rate of immunisation of any kind to be greater in the control group.[31] (This study was continued to incorporate 47 index cases,[32] of whom 45% were vaccinated, usually with DTP, compared with 75% of controls.) In another study of 151 cases of SID 10 of the controls, matched for age and geographical area, had received vaccinations of any kind within 28 days of death of the index case compared with eight of the index cases themselves.[7] In a study of 400 cases of SID controls were matched for age, geographical area, birth weight, and race.[8] Disparities in vaccine uptake between different racial groups were thus controlled for, and it was found that of 373 index cases with known vaccination histories, 39% had received DTP vaccination compared with 57% of the 399 controls.

In a prospective study of 5004 infants who started primary immunisation with DTP, and 4024 who started with diphtheria tetanus (DT), seven died suddenly within six weeks of vaccination.[33] This was no more than was expected by chance. Three of the deaths were in the DTP group (at 4, 20, and 37 days) and four in the DT group (at 2, 5, 37, and 40 days).

## Hypoxaemia as a cause of SID

Hypoxaemia has often been studied, with equivocal results, as a potential cause of SID.[34] In a recent study of 10 infants who suffered severe episodes of hypoxaemia the episodes were caused by prolonged expiratory apnoeas.[35] One of the subjects, with clinically unnoticed and yet frequent episodes of hypoxaemia, was the twin of a SID victim. In contrast to whooping cough itself, in which hypoxaemia is caused by prolonged expiratory paroxysmal coughing, DTP immunisation was not found to increase abnormalities in ventilatory patterns for 30 control infants, 46 infants with unexplained apnoeas, and 33 subsequent siblings of SID victims.[34] This study was unable to quantify obstructive apnoeas, which have been implicated as a further mechanism for SID.[36]

## Conclusion

In conclusion, it is not surprising that a routine procedure in infants such as vaccination has been implicated in SID. Unexpected deaths require explanation and vaccinations are administered to infants at an age of high risk of SID. By chance alone, however, around nine infants a year would be expected to die suddenly in the United Kingdom within 24 hours of DTP vaccination (and, equally, another nine to die during each 24 hours succeeding vaccination). The simultaneous death of twin boys after vaccination was, rightly, regarded as an extraordinary and distressing event, yet it is true that twins are particularly susceptible to SID. Although it is natural to link an unexpected event with its precursor events, coincidences do occur and should be seen in perspective.

I express my thanks to the graphics department, the statistics department, and the secretarial staff at The Wellcome Foundation and to Dr W Shepherd and Dr A H Griffith for their help and encouragement.

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*Archives of Disease in Childhood,* 1987, **62,** 760–763

# Correspondence

## The role of neonatal nurse practitioners: a viewpoint

Sir,

In October 1984 the British Paediatric Association produced a discussion document entitled, '*The Future in Paediatrics and Child Health*. This contained the sentence, 'We wonder if the newborn intensive care nursery could be the place to experiment with nurse technicians in order to reduce the dependence on junior doctors.' In August 1985 the matter was again raised in the editorial of the *Lancet*, the shortfall in senior house officers and registrars could perhaps be made up by neonatal nurses. Deferring to the North American experience where nurse clinicians/specialists were undertaking procedures such as lumbar puncture, exchange transfusion and arterial puncture, it was stated that neonatal nurses, 'might now be asked to consider a greater degree of responsibility in the neonatal intensive care unit, although ultimate responsibility for medical care will remain with the consultants. The British Paediatric Association has (albeit timidly) already suggested this and its members should now act boldly.'

A literature search into the role of the neonatal nurse practitioner showed that this post existed in some units in Canada and the United States and that appropriately trained nurses could replace house officers with no reduction in standards of care. It is not documented as being established in Great Britain, and we are uncertain to what extent practices exist, which fringe on the edge of this role in extended duties of the nurse in neonatal units. Two members of the executive committee of the Neonatal Nurses Association are currently undertaking a national survey of the practice and views of members on this development.

The introduction of this role raises many questions that require deep thought and careful assessment to ensure neonatal care is not compromised. If this role is integral to the future of neonatology, as our medical colleagues have suggested, we must consider the safety and effectiveness of such a role and the method by which it could be introduced. But we must first identify the current dilemmas, which pose grave difficulties for this speciality and are a matter of mutual concern in the United Kingdom.

During the past decade the face of neonatal care has changed dramatically. As medical and scientific understanding of the newborn has increased, the complexity and scope of newborn intensive care has demanded more versatile nursing practice and knowledge. Larger numbers of trained neonatal nurses are required to maintain the quality and continuity of care. Staffing neonatal units with discontinuous nursing resources is now the most persistent and critical area of concern to senior nurses. There is wide recognition of problems needing to be addressed as a matter of urgency. These include inadequate nurse establishments, failure to fill establishments, short tenure posts, and retention difficulties, and a lack of training places. Chronic understaffing has resulted in disproportionate nurse baby ratios, and frustration in role satisfaction. Continuing education and the meeting of training needs is a major shortfall within the speciality. Many senior nurses lack time for nursing developments, research, and creativity in their chosen field.

The starting point must, therefore, be to provide quality care by trained neonatal nurses, albeit to the level recommended by British Association of Perinatal Paediatrics and the Neonatal Nurses Association. To introduce the neonatal nurse practitioner without the safeguard of adequate numbers of trained nurses may impose limitations in delivering sound nursing care. In preparation for a new role it would be important to determine and set our own professional standards and workloads and estimate our own staffing needs. This will entail reappraising use of trained neonatal nurse activity and using a greater proportion in direct patient care, teaching and training, and so forth. We need to consider the place of a consultant neonatal nurse to make nursing decisions regarding the care of the baby, in conjunction with medical decisions. Then, if we are in a position to welcome this role, we must ask questions of our medical colleagues and ourselves. Do we need it? Do we want it? What will be the depth of the role? Technician or Clinician? Will it entail exercising judgment and independent decision making? Who supervises? What place in unit structure, and what type of unit? How do we make up the deficit in trained neonatal nurses? Would it erode training of junior doctors? What update will be required?

A nurse technician who attains competence in technical skills in some invasive procedures is feasible in the current nursing framework. If, however, we are considering a medical change in the traditional delivery of neonatal care, with the introduction of nurse clinicians, we must identify their training functions and practice. We would need a national standard training curriculum at approved centres. The programme must consider the deficit in the basic educational background of nurses and establish a scientific foundation in pathology, physiology, biochemistry etc. To ensure clinical competence skills, and ability to make decisions, the nurse would need supervision and support by senior medical colleagues. Assuming he or she is proficient and the role is beneficial, it must be ensured that this proficiency is maintained.

Neonatal nursing is still in its infancy—in making changes we must be sure we do not lose the few nursing advances we have achieved and are endeavouring to achieve. In the words of John F Kennedy, 'When it is not necessary to change, it is necessary not to change.' If, however, change becomes inevitable, we must move forward with caution.

Presented to Neonatal Nurses Association October 1986

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## Assessment of child abuse

Sir,

Your recent correspondence includes debate on the case conference, the basic instrument of child abuse assessment recommended at Tunbridge Wells A more pertinent topic might be the scenario after deregistration

Unless one hears anachronistic 'go-it-alone' philosophy as in *The Swing of the Pendulum*[1] or the rejection of case conference by the Society of Clinical Psychiatrists, medical megalomania masquerading as purist ethic[2] may go unchallenged Even if one takes the arguments of Drs Chapman and Woodmansey seriously, it is neither practical for child psychiatrists to take the central role regularly, nor acceptable that they decry all multidisciplinary conclusions—perhaps not even attend case conference!

It is apparent that much child abuse care remains parent orientated[3] and that the persistence of far from 'good enough' parenting rather than physical trauma, accounts for the sad sequelae of the acute syndrome for the child, and a legacy of child abuse for the next generation [4] The preoccupation of social work protocol is still with non-accidental injury and expedience, avoiding having too many names on the 'at risk' register, deregistering, and closing the case as promptly as possible—not only for logistic reasons—seemingly without much awareness of, or intention to break, the cycle of underlying emotional deprivation The truth of the latter suggestion is seen at case conference in the absence of any regular account of the abusers' childhood experience of parenting and the facility with which grandparents are proposed to foster abused grandchildren Completing the protocol, deregistration, leaves the child in a dangerous vacuum and encourages parents to evade consultant surveillance, while the passage of years reduces the role of the primary health care team and often sees the end of non-accidental injury and failure to thrive, which may be more related to the child's age than to therapeutic intervention; the child enters school, and, hey presto, his problem is no longer medical but educational The hard data of growth charts and physical injury give way to the subtleties of conduct disorder and intellectual delay—the hiatus in professional contact leaves the educational team unaware, or perhaps unkeen, to pursue the key aetiological factor, continuing emotional deprivation

A handicapped child with rubella embryopathy or cerebral palsy from birth injury at once enters a defined system of assessment and care, formally supervised into the school years By contrast, a child with social handicap, called child abuse, is subject to a flurry of attention after non-accidental injury but very soon drifts into oblivion despite his probable permanent handicap(s) Perhaps rather than struggling to prevent social services departments prematurely deregistering children—perhaps even with a new baby imminent—one should see the paraphernalia of case conference and registration simply as a rather brief management interlude to be followed by further formal consecutive process, recognising the time scale of child abuse and the limited resources of social services departments?

The title 'battered child syndrome' has subserved its purpose Debate on balance at case conference and training of professionals is less important than filling the vacuum after deregistration let the educationalists emerge from their statementing libraries and give us a declaration of intent on child abuse, let their role be formally guaranteed

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## Medium chain triglyceride diet in epilepsy

Sir,

Sills *et al*[1] provide further important information about the use of a medium chain triglyceride diet in epileptic children, but the value of their study would increase with answers to the following questions

1 How common were seizures before treatment?
2 After what period of time did the beneficial effect of the diet become apparent?
3 Over what periods were the post-treatment seizure rates assessed?
4 Was there a length of time following which improvement on continuing the diet was unlikely?

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Dr Forsythe comments:

It is difficult to give a general reply to your questions as four types of seizures were involved.

1 *Astatic myoclonic seizures* (18 children)
  Atypical absences four to 50 per day
  Tonic clonic one alternate day to four to six per day
  Astatic one alternate day to 10 per day
  Eight of the patients had recurrent attacks of status—that is, atypical absences astatic, and tonic clonic seizures.
  *Petit mal* (seven children)
    Four to 10 per day
  *Tonic clonic* (17 children)
    One to 30 or more per week
  *Complex partial* (eight children)
    One to four per day

2 *Astatic myoclonic*
  Of the 18 children included in the study, there are now four who have had a complete remission of seizures for two years A fifth child who had a previous remission for six months, then refused the diet, is now back on the diet and has been seizure free for three months All five children obtained a complete remission of seizures by the 15th day that is, two to four days' starvation plus 14 days' diet (about 50%) When the remaining 13 reached 50–60% diet they were allowed home for two weeks; if no improvement occurred sodium valproate or later nitrazepam was tried If these drugs failed to produce a greater than 50% reduction of seizure frequency they were withdrawn If the diet had not reduced seizures by 50% it was discontinued (see later).
  The same rules applied to absences, tonic clonic, and complex partial seizures

3 Careful records were kept daily of all seizure types and recorded on special record cards as long as they were on the diet. They were seen regularly after withdrawal of the diet.

4 In most cases where we were certain of compliance, we knew within two months if the diet was of value We were not interested in a 50% or less reduction in the frequency or severity of seizures, or both If the parents wanted to continue the diet, we allowed them to do so.

## 'New' fontanometer for estimation of intracranial pressure in the newborn

Sir,

The article by Rochefort, Rolfe, and Wilkinson is seriously misleading. The device described is not new It was shown to the Physiological Society in November 1982[1] by Dr A G Whitelaw and myself. The only difference between their device and mine is that theirs uses two separate tubes while mine uses concentric tubes, which is more convenient Later, I decided that a separate tube for measuring pressure was not essential, provided that the air flow was constant and the zero was checked from time to time—as it should always be A model of the original design, made and used by Cowan and Thoresen,[2] gave clinically satisfactory results The present design is in use in a number of centres, and Kaiser and Whitelaw have reported satisfactory correlations with direct intracranial or cerebrospinal fluid measurements [3]

Dr Rolfe wrote to me in March 1985 describing his modification and I replied, pointing out that he was merely reverting to my original design and explaining why I though a second tube was unnecessary I showed the original device to him some time before it was published, and I was present when it was first put on a baby in Oxford Rowena Oozeer suggested sticking it on with the collodian used for EEG electrodes It worked beautifully and the use of collodion is now standard practice.[3]

The present model has been in use at Northwick Park Hospital for two years, and we hope to publish our results shortly. We have delayed publication so far, because we are still developing our technique and the device is not yet commercially available

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Drs Rochefort, Rolfe, and Wilkinson comment.

It has been recognised for a long time that the design of some fontanometers leads to problems relating to the off-set calibration, and errors resulting from the application force. All these problems were present with Dr Wright's device [1] Discussion, development, and experiment took place to overcome these problems Our previous experience with fontanometers[2] and in the 1970s of devices to measure intraocular, intrauterine, and intravenous pressures non-invasively had given considerable insight into these difficulties. Modifications to design have produced a device that ensures the use of applanation principles, incorporating a guard ring and flow independent pressure measurement At a time when continuous EEG recording was being developed in Oxford the use of collodion was routine and since then has become more widely used.

Our data presented previously (at the Annual Meeting of the British Paediatric Association) and in our paper, when compared with the results from other devices, support our view that the differences in design are crucial to the validity of non-invasive intracranial pressure values At best, previous devices have reflected only trends in intracranial pressure Accuracy is of course vital if a non-invasive method is to be relied on to assess the efficacy of various therapeutic manoeuvres safely and reliably

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# How linear is growth?

Sir,

With great interest we read the article by Wales and Milner on linear growth.[1] We have been using this technique for over three years, and we have surveyed more than 20 000 measurements of the lower leg length (each of these measurements consisting of at least four lower leg length estimations) in more than 300 children, about 80 of these being healthy and measured regularly at weekly or half weekly intervals for periods between three months and two years. Thus we are pleased to see that the authors have found results which are very similar and almost undistinguishable from our data. We have not yet published all our results for several reasons

In the beginning we tried to use knemometry for the assessment of linear growth, hoping to find means to predict linear growth rates in much shorter intervals than hitherto possible. We gave up this aim for exactly the reasons published by Wales and Milner it is not possible. The authors found an irregular pattern of lower leg growth from week to week which was explicable in some children, as they had short illness or underwent tonsillectomy, but not in all of them

We have shown earlier that lower leg growth indeed is non-linear in many children,[2] and this has been confirmed by Wit *et al* [3] Moreover, we have evidence that there is a regular pattern of lower leg growth in many if not in almost all children, which consists of short periods of rapid growth followed by periods of growth arrests every 30 to 55 days, and which we named 'mini-growth-spurts' (Hermanussen M, Geiger Benoit K, Sippell W G, unpublished observations). Therefore, whenever one starts to measure lower leg length at weekly intervals, it has to be shown by the following measurements at what part of the 'mini-growth-spurts' the child momentarily grows in the case of maximal growth velocity extrapolation of such a growth rate will overestimate the mean linear increment of a longer interval, and vice versa. Fig 2 of the article by Wales and Milner provides some perfect examples of 'mini-growth-spurts' that could not have been better measured. If the authors had measured these children longer they would have found not just one single irregular pattern of lower leg growth but most probably something similar to what we termed 'mini-growth-spurts'. They would then have given their article a different title as lower leg growth is non-linear in many cases and thus cannot be used for the assessment of linear growth

As it is much more difficult to measure total body height with comparable accuracy, it still remains to be elucidated whether total body growth is, indeed, linear In view of the scant knowledge on short term body height increments, it is, in fact, questionable, and linearity of total body growth may also be just an assumption, as this was true for lower leg growth before we had evidence to the contrary. The unpredictability of half annual growth rates by monthly measurements as shown in Table 5 of the article by Wales and Milner being rather similar to the findings by knemometry may, indeed, indicate that we overestimate the error of height measurements, and that there is also pronounced non-linearity of total body height increments

In this event all the irregularities of height measurements throughout the years—mostly discarded as 'error of the measurement'—could, indeed, have given some valuable hint which was neglected because it did not fit into our 'weltanschauung' of linearity of short term growth

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# Club foot

Sir,

I was sorry to find in the annotation on club foot no reference to the part which occult spinal dysraphism sometimes plays in the diagnosis and, more importantly, in the management of this malformation of the foot This omission is surprising as so much has been published in the past 20 years, providing evidence of the occasional lower limb deterioration when the spinal lesion is not recognised and attended to. Unilateral club foot, and especially a small foot, are among the most common clues to the presence of a spinal malformation, which should therefore be sought by inspection and (usually) plain radiography of the spine I realise that an annotation is necessarily a brief review of a subject As there was room for emphasising the limited success of treatment of the foot, I think there was space for mentioning one of the occasional causes of failure

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Dr Klenerman comments.

The reason for omitting mention of the neurological aspect of club foot was that I was confining my attention to the so called idiopathic club foot, which is the commonest variety, and in mentioning that diagnosis was easy, I was emphasising the point that prognosis is more difficult in this particular condition

*Archives of Disease in Childhood*, 1987, 62, 764

# Book reviews

**Neurological assessment during the first year of life.** Claudine Amiel-Tison and Albert Grenier Pp 197 £30·00 hardback. Oxford University Press, 1986

This attractive well illustrated and clearly set out volume is in fact an extensive exposition of neuromotor capabilities in spontaneous and elicited movements and postural reactions. Such narrow emphasis is all very well if it succeeds in teaching reliably at a primary care level how to segregate those neonates or older infants who have clinically important minor neurological dysfunction from those who perform up to the expected level There are several paths to this goal but, to the present, the French school's missionary success has been impaired by subtle elitism 'muscle tone . . remains the speciality of the French '

The first part of the book is a recapitulation of the pioneering work of the Clinique Bandelogue, a very welcome introduction for the beginner It now brings us to the phenomenon of 'liberated motor activity' by which automations are suppressed, the impotence of the neck is excluded, and head control is achieved The baby enters a state beyond those of Prechtl, almost mesmerised, but is able to perform definitive motor acts like an older infant—for example, in prehension It may be the most important part of early performance.

The central part of the work sees that 'cold' traditional examinations do not solicit the personal participation of the infant, and the complementary neuromotor examination is enlisted to do so. The process of debugging (sic) is explained, and the repertoire of the liberated state is clearly set out in words and pictures so that much of the techniques could be learned from the printed page Brazelton and the Bobaths are in one's mind, if not much in the bibliography, but few can have given such emphasis to the reaction of lateral abduction of the hip

Finally, the book addresses itself very well to the question of attributing degrees of importance to the various deviant items, above all to identifying those of relatively little importance compared with those of prognostic gravity, drawn from the author's own experience Pitfalls of technique and interpretation may be unthinkable, but there is much of practical value to be learned herein

NEIL O'DOHERTY

**Neurosonography of the Pre-Term Neonate.** Edited by Edward G Grant Pp 116. £46 00 hardback Springer-Verlag, 1986

It is a pity that this excellent monograph starts with an inaccuracy on page 1 It was Cooke (*Lancet* 1979) not Ben-Ora (1980), who first reported the use of sector scanning through the anterior fontanelle of the newborn This is a comprehensive review of the tremendous amount of new information that has accrued since out-side ultrasound scanning was introduced into intensive care nurseries in the early 1980s A result of this development is that in North America sub-specialisation has come about, hence the 'neurosonographer' In the United Kingdom scanning of newborns' heads has been carried out largely by clinicians responsible for their overall care Nevertheless, the authors are right to emphasise as often as they can the need for discussion between all who have any diagnostic or therapeutic role in the care of these patients

A very good section on normal anatomy and an introduction into scanning is well worth reading, and not only by the novice A considerable number of neuropathological and pathophysiological points are emphasised, particularly where these are unique to the preterm brain Excellent sections on germinal matrix related haemorrhage and periventricular leucomalacia is followed by a rather parochial report of a small series of patients followed up in the authors' institution Similarly, it is unfortunate that like so many North American monographs reference is made to only a few reports of work carried out in Europe

This short text does not set out to be comprehensive, and the ultrasound scan appearance of the brain of babies with congenital abnormality and the rarities are understandably not covered The science of neurosonography is still too new for there to be a great deal of experience in these areas The highlight of this book, the best section, relates to the disorder that is of most importance and one with which all neonatal paediatricians should be familiar —namely, periventricular leucomalacia This and all other chapters are liberally illustrated with excellent reproductions of very good photographs A very practical approach to scanning and an interesting discussion about problems still to be resolved rounds off each chapter of this book which I strongly recommend
everyone who has any role in scanning t
newborn brain, whether as operators
as interpretors of the reports of others

ANDREW WILKINSO

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The section on host defence dysfuncti
is marred by a chapter on malnutrition a
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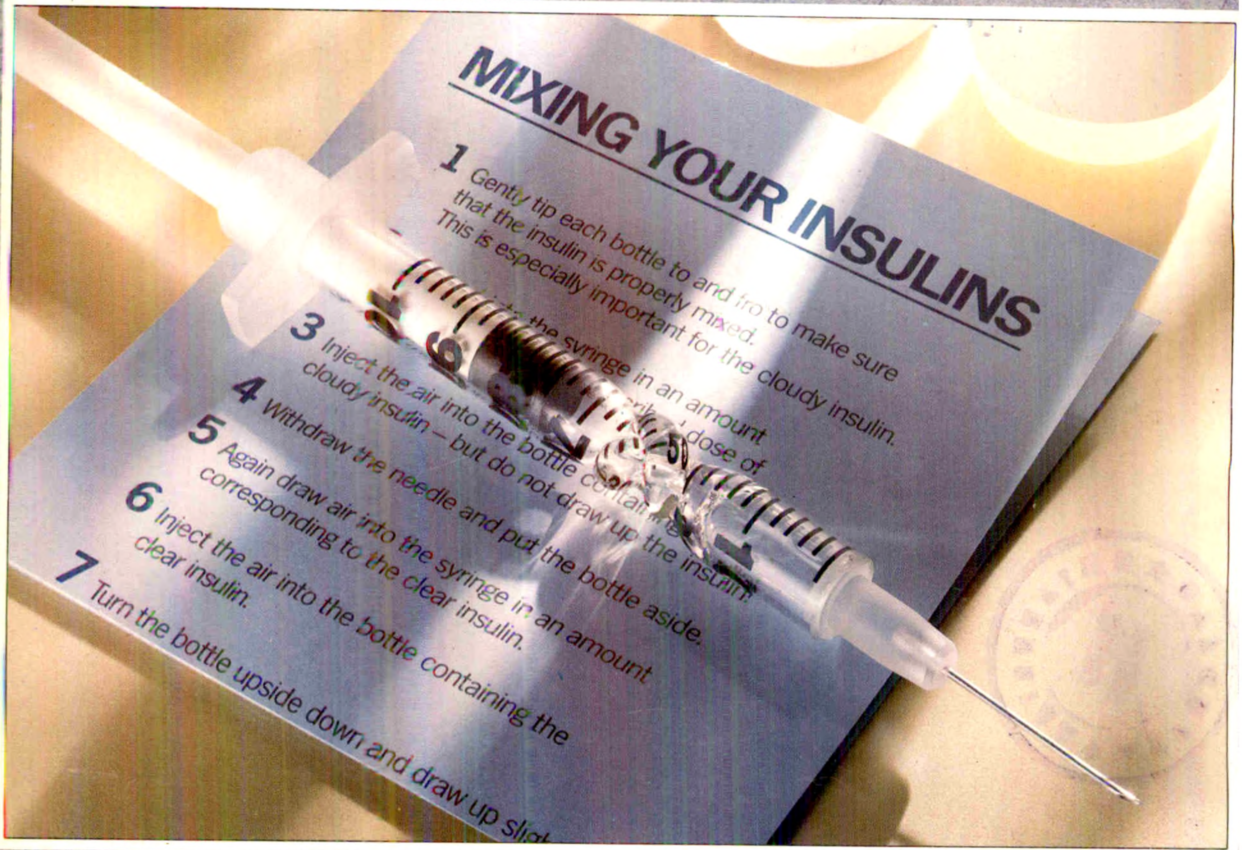
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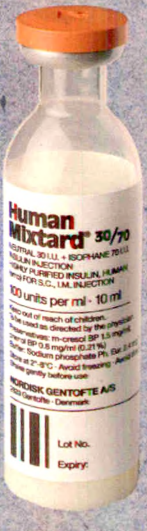

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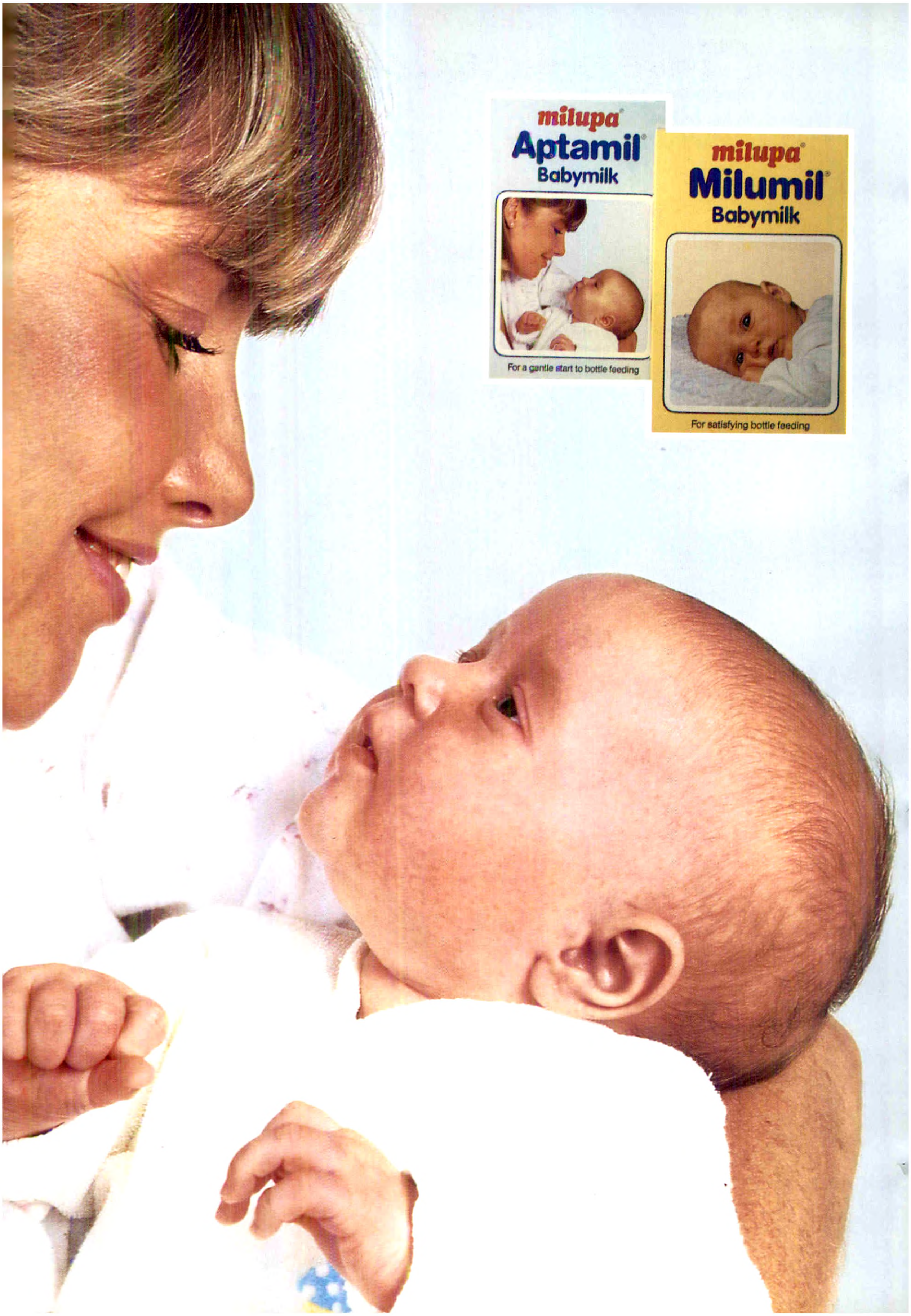
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The James Spence Medal was presented to Professor John Lewis Emery and Dr Frederick J W Miller on 9 April 1987. Professor John Forfar, President of the British Paediatric Association, gave the following citations:

### Professor John Lewis Emery

Early in life John Emery found himself confronted with a career decision between the church, art, or medicine and fortunately chose the latter. He graduated in medicine in the University of Bristol in 1939 and almost at once showed that his primary interest was with children and the problems of childhood disease. Working with the Emergency Medical Service in the early part of the 1939–45 War he was involved in the care of evacuated children. Then began the career in pathology which he has pursued with such distinction since, first at Bristol for five years and then at Sheffield as Consultant Pathologist to the Children's Hospital. It is there that his main life's work has been carried out.

He was the first pathologist to be appointed to the Children's Hospital in Sheffield and over twenty three years there built up a comprehensive paediatric pathology department embracing morbid anatomy, microbiology, haematology and chemical pathology. At a time when in many parts of the country inadequate, usually adult-orientated, pathology services were limiting pathological and therefore clinical understanding of childhood disease and preventing the advances which might otherwise have been made John Emery showed what a paediatric service planned for and devoted to the problems of children could achieve. He played an important part in the many successes which were achieved in the Children's Hospital in Sheffield in advancing understanding of the nature of childhood disease and in developing better methods of management. The energy, the insight into pathology, and the appreciation of the special needs of paediatrics which he has shown have made him one of the founding fathers of paediatric pathology in this country and have established for him an international reputation in the field. Recognising his distinction, the University of Sheffield in 1972 appointed him Professor Associate in Paediatric Pathology, the first such appointment in a British provincial university.

His own research interests have led him through the fields of haematology; developmental anatomy; congenital deformities, particularly hydrocephalus, and latterly unexplained infant deaths. To all of these subjects he has contributed significantly and his original contributions to the literature exceed 200. The number of his co-authors testifies to the extent of his help to others. He has lectured extensively both in this country and abroad and has been a most assiduous contributor to scientific meetings. He was the Frederick Still lecturer of the BPA in 1977.

In the latter part of his career and in his six years of so called 'retirement' he has been associated particularly with seeking an understanding of the problem of cot death. Having explored the pathology of this extensively he has recognised that the traditional methods of pathology cannot alone solve this perplexing problem. With characteristic flexibility of mind he has broken the bonds of traditional practice which bind most pathologists and has emerged as an epidemiologist and social paediatrician of distinction. His contributions to this field continue.

His drive and initiative have also revealed themselves in other ways. Within his profession he has been responsible for initiating the International Paediatric Pathology Association, the Paediatric Pathology Society and the Developmental Pathology Society. He was a Founder Member of the Society for Research into Hydrocephalus and Spina Bifida and a member of the inaugurating committee of the Foundation for the Study of Infant Deaths.

His services and his help have been sought worldwide. On behalf of the World Health Organization he advised on paediatric pathology services in India. The United States asked him to undertake a study of the cot death bereavement services in a number of its states. Both Australia and New Zealand have invited him to survey their infant death material.

Outside his profession the early interest in the Arts which almost deprived medicine of his services has been maintained. He has been associated, at times as President, with a number of literary and fine arts societies in Sheffield and has even been President of a museum society which was not concerned with pathology, the Sheffield Museum Society.

Ungenerously John Emery new describes himself as a 'pathological community paediatrician'. Others would prefer to describe him more accurately as paediatric pathologist, paediatrician, childhood community sociologist, student of the arts, and above all man of deep human sympathy and sincerity to whom this Association is glad to award its highest distinction.

## Dr Frederick J W Miller

Dr Fred Miller qualified from the Medical School of the University of Durham, now the University of Newcastle upon Tyne, in 1934, at a time when paediatrics in Britain was a very inadequately developed specialty. He was one of the pioneers of paediatrics, a member of that distinguished Newcastle trio, Sir James Spence, Donald Court, and Frederick Miller who did so much to establish the pattern and promote the understanding of paediatrics in this country.

Even as an undergraduate in the early 1930s he was influenced by the poverty and childhood disease which he saw around him in the North East of England and he maintained a lifelong interest in social paediatrics. This was recognised in 1955 by his appointment—one which remains unique to this day—as Reader in Social Paediatrics in the University of Durham.

After postgraduate appointments in paediatrics in Newcastle and at Great Ormond Street he showed his early interest in chest disease by a period spent at the Brompton Hospital. He then returned to Newcastle and in 1939 embarked with Sir James Spence on a study of the circumstances surrounding every infant death occurring at home or in hospital in the city of Newcastle. Despite the onset of war this study was completed and published in 1941. It revealed much about the hazards of birth, the risks of prematurity, and the various infections from which children suffered in the first year of life.

Three years of war service as a medical specialist in the army intervened before Dr Miller returned to Newcastle. Now began the classic study of the '1000 families' by himself, Sir James Spence, and Donald Court. This was no short term research but a unique long term study, published in three books, of the pattern and incidence of childhood disease, particularly childhood infections, in a total community. It was a study which brought together in a unified way many elements of the child health service, hospital paediatricians, child health doctors working in the community, nurses and health visitors. It was a lesson on how the child health services could be integrated, a lesson we have still not learned adequately today

Dr Miller, as paediatrician to the Maternity Unit of Newcastle General Hospital, was one of the early neonatologists. At a time when hospital services for the prematurely born infant were very poor he developed a home nursing service for premature infants.

Another of Dr Miller's main contributions to paediatrics was in the field of tuberculosis. When he began his paediatric career tuberculosis was a major scourge of childhood; by 1963 tuberculosis in children in Newcastle had become a rarity. His research and his publications played a not insignificant part in achieving that satisfactory result.

In 1966, at the request of the World Health Organisation, Dr Miller spent nine months in India studying and reporting on the teaching of Child Health in that country. In the subsequent futherance of the projects developed from that study he visited India every year until 1984.

Fred Miller is essentially a caring, concerned paediatrician. The child health problems which he saw all around him concerned him and stimulated him to new endeavours. He threw himself wholeheartedly into attempting to solve them. He recognised the need to measure the nature and size of the problem of childhood disease and addressed himself to it, he saw tuberculosis as a major scourge of children and sought to eradicate it; in Newcastle an infant mortality rate of 91 per thousand in 1937 led him to concern himself with neonatal care and with the development of practical steps to reduce this, when a developing country sought his professional help he responded more than generously.

The enthusiasm with which the announcement of the award of the British Paediatric Association's highest distinction, the James Spence Medal, to Dr Frederick Miller has been received by colleagues young and old in the North East of England and far beyond is a measure of the respect and affection in which he is held; he is recognised as a paediatrician whose career has represented a major contribution to the welfare of children.

**James Spence Medallists**

| | |
|---|---|
| 1960 | Professor A A Moncrieff |
| 1961 | Professor R A McCance |
| 1963 | Sir F Macfarlane Burnet |
| 1964 | Professor L S Penrose |
| 1965 | Dr Cicely D Williams |
| 1967 | Professor R R A Coombs |
| 1968 | Dr Mary D Sheridan<br>Dr D W Winnicott |
| 1969 | Dr G S Dawes |
| 1970 | Professor D V Hubble |
| 1971 | Dr W W Payne |
| 1972 | Dr R C Mac Keith |
| 1973 | Professor C A Clarke |
| 1974 | Dr J Bowlby |
| 1976 | Dr D M T Gairdner |
| 1977 | Professor R S Illingworth |
| 1978 | Dr S D M Court |
| 1979 | Professor K W Cross |
| 1980 | Professor J M Tanner |
| 1981 | Dr Elsie M Widdowson |
| 1982 | Dr D MacCarthy |
| 1983 | Professor J O Forfar |
| 1984 | Dr J W B Douglas |
| 1985 | Dr N S Gordon |
| 1986 | Professor J P M Tizard |

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## *Annotations*

# Balloon dilatation in congenital heart disease

The relief of stenoses in the cardiovascular system without operation has been made possible by the development of balloon catheters that are small enough to enter peripheral vessels yet strong enough not to deform or rupture when inflated to high pressures. The technique was first used for peripheral vascular stenoses and was later adapted for coronary artery stenoses. Dilatation of congenital cardiac lesions became possible with larger balloons after successful relief of congenital valvular and vascular stenoses had been shown experimentally.[1 2]

In many cases of congenital aortic stenosis, and in most cases of stenosis of the pulmonary valve, the valve is thick but pliable and obstruction results from fusion of the valve cusp. Dilatation probably splits the valve commissures in the same way as surgical valvotomy, although tearing of the leaflets has been reported.[3] Dilatation of arterial lesions, on the other hand, is achieved by splitting the intima and part of the media, leaving the adventitia intact.[1 2] The lesions heal by fibrosis, and in the short term restenosis is uncommon.

### Technique

The technique of balloon dilatation is similar for all lesions. Assessment of the drop in pressure across the stenosis is followed by angiography to identify the site of obstruction and allow the correct size of balloon to be selected. An end hole catheter is positioned across the stenosis and an exchange guide wire passed through it. The catheter is withdrawn and the deflated balloon catheter passed over the guide wire to straddle the stenosis. As the balloon is inflated with dilute contrast medium the correct positioning of the balloon is indicated by 'waisting' at the site of the stenosis. When the pressure rises the waisting disappears as the stenosis is relieved. After dilatation haemodynamic and angiographic assessments are repeated to confirm the success of the procedure.

### Indications

In the fairly short period since it was introduced balloon valvuloplasty has become the safe and effective treatment of choice for stenosis of the pulmonary valve after the neonatal period.[4] The results achieved are similar to those of surgical valvotomy, with a 60–75% reduction in valve gradient. Balloons 20–30% larger than the diameter of the valve are safe and produce an appreciably greater reduction in valve gradient than smaller balloons.[5] Residual obstruction at infundibular level is fairly common but resolves completely within a few months provided that the initial valvuloplasty was successful.[5 6] Dysplasia of the pulmonary valve, with thickened, immobile, myxomatous cusps and a small valve annulus, is an uncommon cause of pulmonary stenosis that cannot be cured by valvuloplasty.[3] Critical pulmonary stenosis in the neonatal period is still best treated surgically because valvuloplasty is technically difficult and the valves are often dysplastic.

Surgical relief of aortic stenosis in childhood and adolescence is safe and acceptably reduces the valve gradient. Aortic regurgitation is common but rarely important. Aortic valvotomy in childhood is, however, usually palliative, and most patients later require either repeat valvotomy or valve replacement. Technically, aortic valvuloplasty is similar to pulmonary valvuloplasty. The balloon catheter is introduced through the femoral artery. The balloon size is usually 1–2 mm smaller than the aortic valve ring as measured by angiography or echocardiography. The first report of balloon aortic valvuloplasty in 1984 showed that relief of obstruction compared favourably with surgical results and did not produce appreciable valve regurgitation.[7] If longer follow up confirms these results valvuloplasty may become the first line treatment for children with aortic stenosis.[4]

As surgical relief of critical aortic stenosis in the neonate carries a high mortality we have turned increasingly to valvuloplasty as an alternative. It is, however, difficult to introduce large enough catheters into small femoral arteries. Although coronary balloon catheters have been used successfully in small infants, in our experience they are often too small to produce effective dilatation.

In the Western world congenital mitral stenosis is a rare lesion that is unlikely to respond to balloon dilatation because the valve is usually dysplastic. In developing countries, however, rheumatic mitral valve disease is common in childhood and rheumatic stenosis is caused by fusion of the cusp, which can be dilated by balloon angioplasty.[8] It requires a trans-septal approach to the left atrium and is technically difficult, and its role in the long term management of mitral stenosis in children has not been proved

Both coarctation and recoarctation can be relieved safely and effectively by angioplasty in children over the age of 12 months [9, 10] Angioplasty is not yet a reasonable alternative to surgery in neonatal coarctation because of difficulty of access and because the effect may be transient. Reoperation for recoarctation is not uncommon and has a higher morbidity and mortality, and a lower success rate, than the first operation. Short term results of balloon dilatation already match those of surgery, so that in many centres it is now the treatment of choice.[4]

In coarctation presenting after the age of 12 months balloon dilatation can abolish or reduce the gradient with low morbidity.[10] The stenosis is relieved by disrupting the vascular wall, and the possibility of late formation of an aneurysm has been raised.[11] One published abstract reports the formation of aneurysms at short term follow up. Although these patients were asymptomatic, the aneurysms were excised. In our own experience aneurysm formation is rare and associated with inappropriately large balloons. Our first follow up series of patients with native coarctation treated by angioplasty has been so successful that we are continuing to use it for first line treatment after the age of 12 months

Hypoplasia or stenosis of pulmonary arteries always presents a difficult surgical problem. Balloon angioplasty is feasible, produces relief of stenosis in at least half of these patients,[12] but is technically difficult and carries a small risk to the patient Lock *et al* suggested that balloon dilatation of pulmonary artery stenosis should be considered in children with right heart failure, cyanosis, or supra-systemic right ventricular pressures.[4] Branch pulmonary artery stenosis is often tolerated badly after a Fontan procedure or repair of tetralogy of Fallot, and even a small drop in pressure across the stenosis may be an indication for treatment.[13]

After either a Mustard or a Senning repair for transposition of the great arteries obstruction of the intra-atrial baffle is fairly rare. Surgical correction is difficult and carries a definite risk Balloon dilatation is an attractive alternative.[14] A large balloon is used as these lesions are compliant, and, although this technique probably produces its effect by tearing both the intima of the atrial wall and the fibrosis around the baffle, it is safe, technically straightforward, and preferable to further surgery. Relief of stenosis of a Blalock Taussig shunt by balloon dilatation has been reported and may be an alternative to further operation.[15]

We undoubtedly need time to evaluate the results of balloon dilatation of congenital cardiac and vascular lesions. In pulmonary valve stenosis after the neonatal period, however, balloon dilatation is the treatment of choice. In recoarctation of the aorta, in pulmonary artery stenosis, and in baffle obstruction after atrial surgery the risks of operation are high and the success rate only moderate. In these cases balloon dilatation is now the treatment of choice. In our experience angioplasty for coarctation yields encouraging results, although long term follow up is required before we can be certain that it is free of complications. There is a move towards angioplasty for aortic valve stenosis in both children and adults because the results seem to be as good as, and the risks less than, those of surgical valvotomy.

## Advantages

Balloon angioplasty for congenital lesions is considerably cheaper than surgery, requires no more than three days in hospital (compared with 10–14 after most operations), and avoids both a surgical scar and postoperative complications. It is, however, technically difficult in some cases and requires high quality angiography. For this reason it remains the tool of cardiologists. There is perhaps a place for balloon angioplasty in developing countries for managing and treating children with rheumatic heart disease.

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# Giving drugs per rectum for systemic effect

Suppositories were used as early as 1500 BC by the Egyptians for the local treatment of haemorrhoids and constipation. These suppositories were made by rolling conical chips of wood or bone in honey in which a drug had been boiled until the solution was nearly solid A thousand years later Hippocrates described the use of a suppository made of anise, myrrh, goose grease, and honey as a specific relief for asthma, but it was in Britain in the seventeenth century that the word 'suppositorium' was first used.[1]

The Egyptian technique of using inspissated honey was used until the end of the seventeenth century. Cocoa butter was then used as it liquefied readily on warming and could be mixed with various ingredients; it quickly formed a hard wax and yet conveniently dissolved in the rectum. It was in general use for the next two hundred years, until the introduction of water soluble polyethylene glycols. The importance of the base used in the formulation of a suppository has been reported over the past 20 years.

## Acceptability to the patient

Suppositories are commonly used in certain parts of Europe, but not in the United Kingdom. It is clear from the amount that has been written on the subject that the cultural influences of the parent, the child, and the doctor all have an effect on the acceptability of the treatment Although it is often difficult to get young children to take their medicine by mouth there is no evidence to suggest that compliance is improved if suppositories are prescribed.

## Indications for giving drugs through the rectum

There are several circumstances under which it may be preferable to give a drug through the rectum as opposed to intramuscularly or intravenously; these include circumstances in which the patient is unconscious; nauseated or vomiting; or if oral intake is forbidden immediately before operation. First pass elimination in drugs with a high hepatic clearance may also be avoided in this way.

## Absorption from the rectum

The rectum is drained by the superior, middle, and inferior rectal veins. The superior rectal vein drains through the inferior mesenteric vein into the portal vein, whereas the inferior and middle rectal veins drain directly into the inferior vena cava through the internal pudendal and internal iliac veins. There are extensive anastomoses between the rectal veins.

When a drug is taken orally and absorbed from the gastrointestinal tract, it enters the portal vein and is metabolised in the liver. If it is one which is principally broken down in the liver—for example, morphine, hydralazine, or propranolol, it does not achieve its optimal effect when taken orally. If it is given through the rectum however, better absorption and greater systemic effect may be achieved.

The mechanism of rectal absorption is probably similar to that of the upper part of the gastrointestinal tract, despite differences in pH, surface area, and fluid content. The use of surfactants can increase the amount of absorption of a drug from the rectum; they can, however, damage the rectal mucosa and so their use requires further investigation. The effects of different pharmaceutical formulations of the suppository may also affect the availability of the drug, and this has been particularly well documented concerning paracetamol.[2] A practical problem with the use of suppositories is premature expulsion, which may result in inadequate absorption.

## Specific drugs

**Anticonvulsants.** A solution of diazepam given rectally is effective for treating convulsions in children, therapeutic plasma concentrations being obtained within four minutes.[3] There is a considerable delay in the achievement of a therapeutic plasma concentration of diazepam after the use of suppositories, and with the introduction of rectal solutions there is no indication to use suppositories The two major indications for the use of diazepam solution rectally in children are by parents at home for children who suffer from either febrile convulsions or recurrent, poorly controlled epilepsy, or by a doctor when immediate intravenous access is not technically possible. It is preferable to give diazepam intravenously in a paediatric unit or in an accident and emergency department, as therapeutic plasma concentrations are more readily achieved by this route. Although clonazepam can be administered rectally, it takes up to 20 minutes for therapeutic plasma concentrations to be achieved.

Paraldehyde used to be given rectally in the United States of America, but we now know that rectal absorption of paraldehyde is considerably slower than if it is given either intramuscularly or orally and it is therefore unsuitable for treating epilepsy. Paraldehyde can also irritate the rectum and large intestine when given rectally, and decomposed paraldehyde has caused perforation of the large bowel. It is far safer to administer it as a deep intramuscular injection

**Antibiotics.** Metronidazole suppositories are effective in reducing the postoperative anaerobic wound infections in children with appendicitis[4] The suppositories are considerably cheaper than the intravenous infusion, and pharmacokinetic studies have shown that they produce therapeutic plasma concentrations If, however, the child has an intravenous line, it is preferable for the drug to be given intravenously.

**Paracetamol.** Paracetamol is used mainly as an antipyretic in children. Although paracetamol suppositories are not commercially available, most hospital pharmacies produce their own. The formulation of the suppository influences the availability of the paracetamol, and there are few data on the bioavailability of the paracetamol in suppositories in different hospitals. The major clinical indication for giving paracetamol rectally is if a child is admitted with an acute febrile convulsion, and the paracetamol can be administered before the child wakes up. Paracetamol is also useful in suppository form for children who have fevers associated with vomiting.

**Other drugs.** Theoretically, morphine is an ideal drug to be given rectally as it is extremely well absorbed. A pharmacokinetic study following rectal morphine (0·15 mg/kg) in propylene glycol, however, showed plasma concentrations that were inadequate for pain relief.[5] Rectal theophylline has been used for children with asthma, but with the advent of oral slow release theophylline preparations suppositories have been superseded. There have been several reports of one or more drugs given rectally as premedication before operation.[5] [6] Unfortunately, little data were given on the acceptability of the rectal compared with the intramuscular route.

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# Are intelligence tests outmoded?

Most doctors know little about clinical and educational psychologists' areas of expertise; although most do know that they carry out intelligence tests Now, just when doctors have accepted the intelligence quotient (IQ) as a measure of intelligence, psychologists seem reluctant to use the term. Why? Is something wrong with the concept of IQ? Are IQ tests outmoded?

## The history of IQ tests

According to Eysenck, the ancient Greeks introduced the concept of intelligence.[1] They regarded it as the potential to think, reason, and solve mental problems, and they differentiated it from a person's observed behaviour. Centuries later tests of intelligence evolved, the first widely used one being Binet's, which was developed in France in the early 1900s.

Binet's original test still exists today, recently restandardised as the Stanford-Binet test of intelligence. The original purpose of the test, which was designed at the request of the French education authorities, was to select children who were having difficulties in learning so that they could have extra tuition. Binet himself believed that ability could change, but many of those who adopted the idea of testing IQ believed that intelligence was inherited and essentially unalterable. This belief was particularly strongly held by the eugenicists, who proposed that 'superior' people should be encouraged to procreate while 'inferior' people, such as criminals, epileptics, alcoholics, and imbeciles, should be discouraged from doing so Indeed, in more than 30 American states in the early twentieth century there was legal provision for such people to be compulsorily sterilised.[2]

## More recent IQ tests

Since Binet's time other IQ tests have been developed. They are all designed to measure intelligence, even though there are still major disagreements between psychologists about what intelligence is.[3] The tests include series of tasks, both language based and language free. During the development of a test many people (children or adults, depending on the age range to be tested) are given the same tasks, and scoring is adjusted so that someone who obtains a raw score exactly in the middle of the range will be assigned a scaled IQ score of 100—that is an average IQ. Most test scores have a standard deviation of 15 so that in theory, assuming a normal distribution of scores, about 67% of the population will achieve scaled scores between 85 and 115 (one SD below and above the mean) and about 95% will score between 70 and 130 (two SD below and above the mean), leaving about 2·5% at the extreme ends of the distribution curve. This is not, however, as straightforward as it sounds; for instance, IQs of given populations do not conform exactly to a normal distribution. In addition, the composition of the standardisation group is crucial: if, for example, only highly intelligent people are tested during the standardisation, when the rest of the (untested) population is assessed most of them will score below average. The converse also holds true, and this makes the interpretation of IQ scores difficult. Most importantly, it means that if groups of people are tested who were not represented in the standardisation sample their IQ scores can be interpreted only as indicating that they are above or below the mean of the standardisation sample, rather than above or below the mean of the population of which they are a part. The mean IQ of a population is thought to rise by about 0·3 IQ points each year Thus if tests with out of date standardisation scores are used children's IQ are overestimated if their scores are thought to compare to those of the current population (the original mean development quotient score, on the Griffiths scale was 100, but the current mean is 110 or more)

## What do IQ tests measure?

IQ tests measure a person's performance on a series of tasks, in a particular setting, on a particular day, with a particular tester. Whether the person's score reflects his or her underlying ability, (in comparison with others) to think, reason, and solve mental problems will depend on many factors One of these is the degree to which such a score can be generalised for different days, settings, and testers for the person in question. Another important factor is the degree to which scores can be generalised for particular tasks. A third factor is the person's motivation.

Most well constructed IQ tests contain information about the short term reliability of scores in the test manual, this is in the form of test/retest checks to show the degree to which people's scores on one day correlate with their scores on a later day Over short periods the correlations are usually good—for example, in the Weschler intelligence scale for children (revised) (WISC–R) the test/retest reliability over four weeks for the full scale IQ was about 0·95. Conventional IQ test manuals also provide figures for the standard error of the test scores—that is, the error attributable to 'imperfect measuring procedures'. This allows the tester to state that, for example, the 'true' IQ score will lie between stated limits on 95% of occasions. Thus if a child aged 9½ has a score of 90 on the WISC–R it is 95% certain that his 'true score' will lie between 84 and 96 (his actual score ± twice the standard error). Other tests, such as the McCarthy scales, Weschler preschool and primary scale of intelligence (WPPSI), Weschler adult intelligence scale (WAIS), and British ability scales (BAS), have similar margins of error. All these tests include specific instructions to try to reduce the variations between testers, and the level of error may be expected to be higher if the tester deviates from the procedure laid down in the manual—for instance, in how much practice he allows on a test item, or how much help he gives on an item.

The degree to which a person's scores may be generalised for different tasks is more complicated. One way of examining this issue is to look at the correlations between people's scores for different IQ tests. To the uninitiated the tasks in different IQ tests look similar, but the published correlations between IQs using different tests vary between 0·45 and 0·95. Thus even though those who construct the tests try to include a wide variety of tasks and do their best to avoid using tasks that depend on a person's cultural experience (something that many psychologists think is impossible), a person's IQ score obtained with one IQ test can differ considerably from the score obtained with a different test.

Finally, one of the variables that intervenes between a person's underlying capacities and his behaviour (and hence IQ score) is motivation. Disaffected youths for example, may not be motivated to try to complete tasks, nor may children with whom the tester has poor rapport because of differences in class, race, culture, or personal affinity.

## Changes in IQ over time

Do people have IQs in the same sense that they have blue eyes? It seems to be a common belief among the general population that a person's IQ changes little over time. Research, however, suggests that this is not so. If people are given IQ tests on several occasions, years apart, the usual finding is that the scores correlate positively, with higher correlations when the intervals between tests are short and the lowest correlations between tests carried out in infancy and those done in later childhood. The reasons for the low correlations between infant test scores and those later in childhood are controversial. A major factor is probably that most tests of infant ability concentrate on tasks assessing motor skills; more recently developed tests that concentrate on the infant's ability to deal with information are better predictors of later IQ. Even when the correlations between tests are high, however, Hindley and Owen have shown that quite wide variations in IQ are not unusual.[4] In their longitudinal British study they found that between the ages of 8 and 17 the scores of half of their subjects changed by 10 points or more, and one quarter changed by 17 points or more. The correlation between the scores at 8 and 17 years was 0·74. This, however, was a study of a sample of children in London and entailed two different IQ tests. Correlations for samples from more stable populations may change less, especially if the same or similar tests are used. Yule *et al* found a correlation of 0·86 between scores for children in the Isle of Wight at 5½ years old on the WPPSI and 16½ years old on the WISC–R.[5]

## Genetics, environment, and IQ

The changes in IQ described above imply that an IQ score is not a constant that is associated with a person for life. What produces these alterations? Changes in a person's environment seem to have major effects on IQ. Studies by Dennis, for example, showed that normal children placed in orphanages in Lebanon before 1956 had IQs of only about 50, presumably as a result of neglect. Those adopted into ordinary families before the age of 2, however, regained a normal IQ. Many other studies have shown that a variety of environmental factors can affect IQ, including social class, maternal responsiveness, the provision of toys, the arrival of siblings, and schooling. Which of these factors is most important is a matter for debate, but, even though there may be some inheritance of intelligence, the effect of environmental factors can be substantial.[7 8]

## The uses of IQ tests

One of the major uses of IQ tests in the past has been to assess children in ordinary schools who were having difficulties in keeping up with their classmates. At one time strict application of IQ tests consigned those with an IQ below a certain score to special schools. Psychologists have become increasingly unhappy about this because of the accumulation of evidence on the degree of error in the tests, the importance of comparing like groups when interpreting the scores (particularly for ethnic minorities), the changes in IQ with time, the fact that different IQ tests are not comparable, and the educational and social effects of attending a special school.

Does this mean that IQ tests are not useful? This necessarily prompts the question: useful for what? There are, as yet no better tests of general cognitive function, so that for certain clinical purposes (such as distinguishing specific reading retardation from overall developmental slowness), and some research questions (such as whether a group of children with phenylketonuria, for example, are in the normal range of general cognitive development) IQ tests may continue to be used. For many other problems psychologists may well turn to tests of specific abilities rather than to general IQ tests. In either instance, what is most important is that those who interpret the scores should know what they mean, what range of error is possible, and how the scores may change over time.

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***Original articles***

# United Kingdom multicentre clinical trial of somatrem

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SUMMARY In a multicentre clinical trial 54 children aged 4·0 to 17·3 years, who had growth hormone deficiency that had not previously been treated, were given biosynthetic methionyl growth hormone (somatrem) 4 units three times a week by subcutaneous or intramuscular injection for one year. Height was measured every three months for at least one year before and during treatment. Forty two patients responded to treatment with an increase in growth of >1·5 cm/year. The remaining 12 who grew more slowly were less obviously short and had a higher pretreatment growth than those who responded. The three who responded and the one who did not had undergone therapeutic spinal irradiation before starting the drug. If a whole year's pretreatment growth rate of <5 cm/year had been used as a diagnostic criterion the prediction of those who responded would have slightly improved. About two thirds of the patients developed antibodies against growth hormone and *Escherichia coli* protein; these were, however, of low and fluctuating titre and binding capacity, and did not influence the response to treatment. No adverse side effects were encountered. We conclude that somatrem is a safe and effective alternative to pituitary growth hormone.

The development of techniques for the large scale production of biosynthetic methionyl growth hormone (met-GH, somatrem) was welcomed, because of the limited availability of human pituitary glands from which growth hormone was extracted. Early batches of somatrem were contaminated with appreciable amounts of *Escherichia coli* protein,[1 2] and it was not until 1984 that a multicentre trial of somatrem was possible in the United Kingdom. In May 1985 human pituitary growth hormone treatment was withdrawn and somatrem was granted a product licence later that year.[3] This paper reports the results of a one year trial of somatrem, a preliminary account of which has already been published.[4]

## Patients and methods

Children with growth hormone deficiency who fulfilled the criteria of the Health Services Human Growth Hormone Committee[5] were eligible for the trial, which entailed treatment with somatrem (Somatonorm, KabiVitrum, Stockholm, batches 81491, 89682, 53809, and 57091) 4 units three times a week by subcutaneous or intramuscular injection. Patients had not been previously treated with growth hormone, but all had been monitored for their growth rate for one year or more. The trial protocol was approved by the local ethical committee at each participating centre and consent was obtained from the parents in each case.

Patients were seen at three monthly intervals when height, both standing and sitting, was measured by standard techniques and samples of blood and urine were collected. Urine was tested for the presence of protein, blood, and glucose using dipstick methods. Blood was analysed at each centre for haematocrit, white cell count and differential, haemoglobin, blood glucose, serum albumin, urea, and creatinine concentrations; and alkaline phosphatase, glutamic oxaloacetic transaminase, and glutamic pyruvic transaminase activities by standard laboratory methods. Serum was stored on each occasion at −20°C and titres of antibodies to growth hormone measured by radioimmunoassay,[6] and to *E. coli* protein by an enzyme linked immunosorbent

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Participating centres Childrens Hospital, Sheffield, Addenbrooke's Hospital, Cambridge, General Infirmary, Leeds, Royal Belfast Hospital for Sick Children, Belfast, University Hospital of Wales, Cardiff, Queen's Medical Centre, Nottingham, Royal Victoria Infirmary, Newcastle upon Tyne, St Mary's Hospital, Manchester, The Children's Hospital, Birmingham, Royal Hospital for Sick Children, Bristol St Bartholomew's Hospital, London Alder Hey Children's Hospital, Liverpool, Leicester General Hospital, Leicester

assay.[7] The titre of antibodies to growth hormone was expressed as the logarithm of the serum dilution which bound 50% of a tracer amount of growth hormone labelled with $I^{125}$ in a radioimmunoassay—for example, 50% binding at a serum dilution of 1/100 was expressed as a titre of 2·0. The titre of antibodies to *E. coli* protein was similarly expressed. The binding capacity of antibodies to growth hormone was calculated from Scatchard plot analysis and expressed as mg/l. *X*-ray pictures were taken for the determination of bone age by the TW2 method before treatment, and six and 12 months later. Not all laboratory and radiological measurements were made for each child on every occasion.

Between October 1984 and July 1985, 63 children were enrolled in the trial at 13 centres. Nine patients were subsequently omitted from analysis: two did not start treatment and seven stopped after three or six months. Table 1 gives a diagnostic classification of the 54 children treated with somatrem for one year. There were 33 boys and 21 girls, aged between 4·0 and 17·3 years at the start of treatment. Of the 11 patients in whom the cause of the hypopituitarism was known, nine had received either therapeutic or prophylactic cranial irradiation and two had craniopharyngiomas.

Patients were judged to have responded if the growth rate over one year of treatment increased 1·5 cm/year or more over the preceding year. Heights were converted into standard deviation scores by reference to published tables.[8] Comparisons of growth rates between different subgroups and the possible effects of somatrem on laboratory measurements were analysed by Student's *t* test or non-parametric methods, as appropriate.

## Results

**Clinical.** Forty two of the 54 patients responded to treatment with a satisfactory increase of growth rate. Of those who did not, one had multiple idiopathic pituitary hormone deficiency, was in late puberty, and had a low growth rate (1·80 cm/year) before treatment; this did not change after treatment. Nine of the other 11 had been diagnosed as having isolated idiopathic growth hormone deficiency but had pretreatment growth rates of 5·0 to 9·6 cm/year. Side effects due to somatrem were not seen in any patient. Twenty six episodes of intercurrent illness were reported in 20 patients. These varied from upper respiratory tract infections and undiagnosed abdominal pain to naevoid basal cell carcinoma of the neck and trunk (Gorlin's syndrome).

**Growth.** The heights of children with non-idiopathic growth hormone deficiency were less abnormal before treatment than those of children with idiopathic growth hormone deficiency, but the mean growth rate of all the diagnostic subgroups was similar both in the year before treatment and during treatment (Table 1). As there were no significant differences among the subgroups, the group is considered together in further analyses. The change in mean growth rate from 4·6 to 8·3 cm as a result of treatment with somatrem is potentially misleading, as the figures include patients who did not respond and patients who had previously undergone spinal irradiation and who responded to treatment mainly by lower segment growth. Subdividing the group shows that the mean (SD) height of those who responded was −3·25 (0·98) standard deviation score, whereas that of those who did not was −2·44 (1·06) standard deviation score. The growth rate of those who did not respond was greater before treatment than that of the responders (Figure). Only three of 12 who did not respond had a growth rate of $\leqslant$5 cm/year before treatment, and seven of 42 who did respond had a growth rate before treatment of more than 5 cm/year. This simple criterion thus identified correctly 44 of 54 (81%) of the patients.

The mean (SD) increase in growth rate in the 42 who responded was +4·6 (1·8) cm/year. One patient

Table 1 *Mean (SD) height, growth rate, and diagnoses of children treated with somatrem*

| | *No of children* | *Height before treatment (SDS)* | *Height after treatment (SDS)* | *Growth rate before treatment (cm/year)* | *Growth rate during treatment (cm/year)* |
|---|---|---|---|---|---|
| Idiopathic | | | | | |
| Isolated growth hormone deficiency (total) | 31 | −3·32 (1·10) | −2·58 (0·93) | 5·1 (1·8) | 9·0 (2·2) |
| Isolated growth hormone deficiency (partial) | 5 | −3·15 (0·78) | −2·72 (0·77) | 3·6 (1·1) | 7·7 (2·0) |
| Multiple hormone deficiency | 7 | −2·75 (0·80) | −2·04 (0·91) | 3·8 (1·2) | 7·6 (3·0) |
| Non-idiopathic | | | | | |
| Isolated growth hormone deficiency | 7 | −2·68 (1·05) | −2·43 (1·11) | 4·4 (2·3) | 6·9 (2·0) |
| Multiple hormone deficiency | 4 | −2·29 (0·93) | −1·88 (0·95) | 3·8 (1·8) | 7·0 (1·5) |
| Total | 54 | −3·08 (1·05) | −2·45 (0·94) | 4·6 (1·8) | 8·3 (2·3) |

SDS is standard deviation score

who had received spinal irradiation failed to respond, and when the other three irradiated patients were omitted the mean (SD) increase in growth rate of the remaining 39 was +4·8 (1·8) cm/year. Growth in the upper and lower segments of the four children who had received spinal irradiation was: 1·2+5·3=6·5; 2·4+2·5=4·9; 3·7+5·9=9·6; and 1·7+2·0=3·7 cm/year, respectively. The mean (SD) change in bone age during treatment was +1·23 (0·82) years (n=35). Six children who received their treatment by intramuscular injection had a mean (SD) growth rate of 8·4 (1·0) cm/year. This did not differ significantly from that of 32 who had their drug given by subcutaneous injection: 8·5 (0·4) cm/year

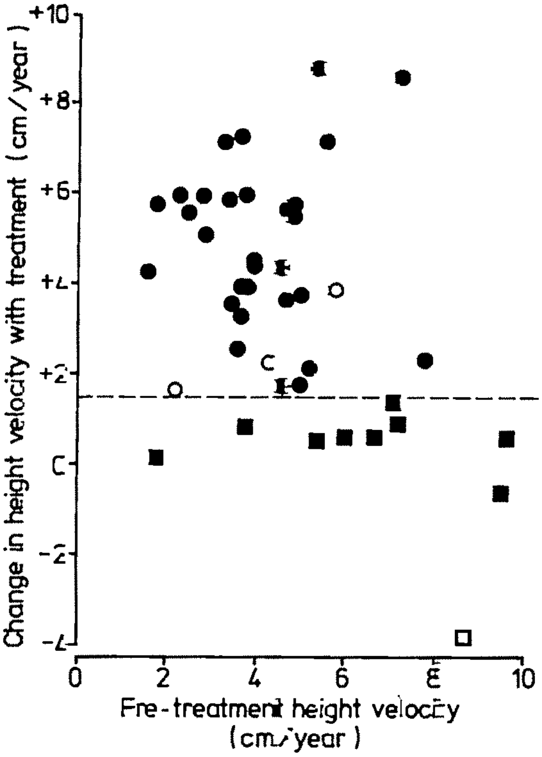

Figure *Change in growth rate after treatment with somatrem for one year compared with that before treatment* ● = *patients whose growth rate increased by >1·5 cm a year,* ■ = *patients who did not respond to somatrem,* ○ = *patients who underwent spinal irradiation*

**Antibodies.** Most children were tested for antibodies to growth hormone and *E. coli* protein at each visit (Table 2). Before somatrem treatment no antibodies to growth hormone were found, but 39% of children had antibodies to *E. coli* protein. As treatment progressed the number of children with antibodies to growth hormone rose, after six months it stabilised with about two thirds having antibodies. The percentage of children positive for *E. coli* protein also rose to a maximum of 87% at six months, but then declined to 67% at 12 months. The titre of growth hormone antibodies was low, the highest value being 3·8, and that of *E. coli* protein antibodies also low, the highest being 0·7. Only two sera from different patients had growth hormone binding capacities above 1 mg/l (Table 2), and in each case the value subsequently fell Of the 175 sera examined between three and 12 months after the start of treatment, only 54 had detectable binding capacity (≥0·01 mg/l). There was no trend to increased binding capacity with length of treatment.

Growth rates were analysed after subdividing the children into those with a log titre of antibody to growth hormone of less than or greater than 1·1 The mean (SD) growth rate of 14 patients with a log antibody titre of less than 1·1 was 7·9 (0·8) cm/year, which did not differ significantly from that of 34 children with a titre of more than 1·1, 8 1 (0·3) cm/year. There was no correlation between binding capacity and growth rate. In particular, the patients who did not respond to somatrem had low or no binding capacity.

**Laboratory tests.** No clinically important change

Table 2 *Presence of antibodies against growth hormone and E coli protein in children before and during treatment with somatrem*

| | *Time (months)* | | | | |
|---|---|---|---|---|---|
| | *0* | *3* | *6* | *9* | *12* |
| Antibodies against growth hormone | | | | | |
| No of patients | 42 | 44 | 47 | 39 | 47 |
| Percentage positive | | 57 | 70 | 72 | 64 |
| Mean log titre (SD) | | 1 0 (0 9) | 1 3 (1 0) | 1 5 (1 1) | 1 5 (1 3) |
| Maximum binding capacity (mg/l) | – | 0 38 | 1 60 | 2 60 | 0 86 |
| Antibodies against *E coli* protein, | | | | | |
| No of patients | 44 | 45 | 48 | 39 | 48 |
| Percentage positive | 39 | 56 | 87 | 79 | 69 |
| Mean log titre (SD) | 0 1 (0 2) | 0 1 (0 2) | 0 2 (0 2) | 0 2 (0 2) | 0 2 (0 2) |

occurred in the result of any haematological or biochemical test. Haematuria and glycosuria were not seen, but occasional slight proteinuria was recorded, this did not occur consistently in any patient.

## Discussion

The United Kingdom multicentre clinical trial is the largest to evaluate somatrem using only one regimen. This permitted a critical assessment to be made of its antigenicity, as well as a careful analysis of the response to treatment in each diagnostic subgroup.

The somatrem used in the trial contained 2–4 ng *E. coli* protein per phial, appreciably less than earlier preparations[9] Although antibodies to growth hormone and *E. coli* protein developed in most patients, titres were low and fluctuated. More importantly, no patient developed a growth hormone antibody binding capacity (>7·5 mg/l) which could have inhibited the therapeutic effect.[10]

It is usual to report the results of treatment with growth hormone in terms of growth rate (cm/year), but this takes no account of the scatter of age, the potential for catch up (which is related to the duration of growth hormone deficiency), or the fact that some patients cannot respond fully because of previous spinal irradiation. For these reasons the results of this study were subdivided by diagnosis and by therapeutic response. The definition of response to treatment was based on the clinical experience of the Health Services Human Growth Hormone Committee. The cut off point, an increase in growth rate of more than 1·5 cm/year, was set deliberately low to avoid inappropriate exclusion.

Of the 12 who did not respond, nine came into the categories of idiopathic total or partial growth hormone deficiency, but had relatively high growth rates. This illustrates the poor diagnostic discrimination of biochemical tests. In contrast, the simple criterion of a whole year of growth rate before treatment of less than 5 cm/year would have predicted response marginally better. It was not possible to refine this predictor by conversion into standard deviation scores, as standards based on chronological age are inappropriate. As a group those who did not respond were less obviously short than those who did, but this information was of no help in sorting patients according to the aetiology of their growth hormone deficiency.

Examination of the diagnostic subgroups showed that patients with idiopathic growth hormone deficiency were shorter than those with overt hypothalamo-hypophyseal disease, presumably because other symptoms made the latter group seek medical attention earlier. There were no significant differences among groups in response to somatrem treatment, and when those who did not respond and patients with spinal irradiation were excluded, the mean change in growth rate due to somatrem was similar to that seen in other trials despite differences in dose regimen.[11 12] The use of a standard dose three times a week, irrespective of body size, ensured a uniform treatment protocol for all children. Response to treatment was not analysed by dose/kg body weight because, to make sense, the height velocity should be transformed into standard deviation score, and this was not possible.

The lack of adverse clinical or laboratory side effects was gratifying but not unexpected in the light of experience with earlier preparations of somatrem and pituitary growth hormone. We conclude from this study that somatrem is a safe effective alternative to human pituitary growth hormone for the treatment of children with growth hormone deficiency.

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# Early acquisition of cytomegalovirus infection

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SUMMARY Two hundred and fifty three infants were screened for cytomegalovirus (CMV) in the urine at birth and were followed up at regular intervals for one year. Twelve per cent (of 249) were excreting virus at 3 months, and 20% (of 234) at 12 months. In all cases infection was subclinical. The major factors determining risk of acquiring infection were the mother's serological state and whether the infant was breast fed. There was no association with social class, mother's age, or whether the child had been in a special care baby unit or a postnatal ward. By one year 33% (of 123) of infants of seropositive mothers had acquired CMV infection compared with 4% (of 123) born to seronegative mothers. Twenty per cent (17) of seropositive women who breast fed had virus isolated from their breast milk on at least one occasion, and 76% (13) of their infants became infected. In four mother-infant pairs comparison of CMV isolates from the mother's milk and the child's urine was made by restriction endonuclease digestion; in each pair infection had apparently occurred with the same strain of virus. All 13 infected infants followed up for three years were still shedding virus.

Infection with CMV is common in infancy, and virus shedding persists for years. Congenital infection cannot be distinguished from acquired infection unless the presence of CMV in the urine is identified within three or four weeks after birth, even when clinical problems suggestive of congenital infection are present.

Congenital cytomegalovirus (CMV) infection is the most common intrauterine infection and an established cause of handicap.[1-4] The prevalence of congenital infection in the United Kingdom is 3–4/1000 live births.[5] Follow up studies have shown that 10% of congenitally infected infants will have permanent neurological sequelae.[4] In contrast to congenital infection, the prevalence and importance of CMV infection acquired after birth has not been well documented in the United Kingdom. In September 1982 a prospective study was set up to investigate the prevalence of CMV infection acquired in the first year of life in a London population and to investigate its role, if any, in the cause of childhood illness. We describe here the acquisition of CMV infection in the first year of life and relate this to maternal CMV antibody state and to possible sources of infection, such as breast milk.

## Patients and methods

**Study population.** During one year from 1 September 1982, 269 infants from the Charing Cross Hospital maternity unit were enrolled in the study. They comprised all infants admitted to the special care baby unit for more than 24 hours (102 infants) and 167 randomly selected from the postnatal wards. All children were screened at birth for congenital infection, and during this period two infants had CMV in their urine and were therefore congenitally infected. They were not enrolled. Of the 269 infants enrolled, three from the postnatal wards and 13 from the special care baby unit were lost to subsequent follow up: 11 had left the district or were transferred to other hospitals, four died while in the special care baby unit, and one mother refused to participate in the study. Thus 253 infants were available for follow up.

**Infant follow up.** A throat swab and a urine sample were taken from each infant in the first week of life and cultured for CMV. Samples were inoculated in duplicate into human embryonic lung cells, and CMV was identified by the appearance of typical cytopathic effects. Weekly urine samples were collected from all infants while they remained in hospital.

Details of all blood transfusions to the infants were recorded and aliquots of blood from each transfusion tested for antibodies to CMV by complement fixation test.

After discharge from hospital arrangements were made for the research nurse (CJ) to visit the infants at home or see them in the paediatric clinic at six weeks, three months, eight months, and one year. In fact, the visits were on average at eight, 15, 37, and 55 weeks. At each visit a urine sample was taken and cultured for CMV. At the one year visit all children were examined by a paediatrician (KP), who carried out a Griffiths developmental assessment. At this visit a fingerprick blood sample was taken on to absorbent blotting paper and tested for antibodies to CMV by radioimmunoassay.

Of the 253 infants followed up to six weeks, 249 were seen at three months, 247 at eight months, and 234 at one year. In a separate study to check for how long CMV was present in the urine the 46 infected infants were followed up for longer periods, 13 for up to 36 months.

**Information about mothers.** As part of a continuing prospective study of CMV infection in pregnancy a short questionnaire was completed by interview for all women attending the antenatal clinic for the first time.[5] Information on age, marital state, parity, race, country of origin, previous or current occupation, and husband's or partner's occupation was obtained. In addition a blood sample was taken and tested for the presence of antibodies to CMV by complement fixation test. A dilution of 1/10 was taken to indicate previous infection. Seronegative women were retested during pregnancy and at term to identify those in whom seroconversion occurred.

Breast milk samples were collected weekly from mothers while their infants remained in hospital and subsequently at each follow up visit if breast feeding was continued. These samples were inoculated into human embryo lung cells after they had been spun down at 4000 rpm for 20 minutes and the creamy layer had been removed.

Viral DNA of CMV isolates from the breast milk of four mothers and the urine of their infected infants was typed by restriction enzyme analysis.[6]

**Statistical analysis.** The effect of breast feeding and the mother's serological state on CMV acquisition was assessed by life table analysis. Four periods at risk were considered: 0–8, 9–15, 16–37, and 38–55 weeks. It was assumed that CMV has a three week latent period, as the earliest evidence of infection was found in urine samples taken when infants were 3 to 4 weeks old. Thus infants were considered to have been at risk for five weeks before the visit at the end of the eighth week. Separate life tables were constructed by adding time at risk before the end of breast feeding to the breast feeding life table and subsequent time to the non-breast feeding life table. In this way four life tables were constructed, one for each combination of the mother's serological state and the feeding method. Mantel-Haenszel odds ratios and their 95% confidence intervals were computed, stratified by time period.[7] The odds ratio associated with maternal seropositivity (for example) is the amount by which seropositivity multiplies the odds of acquisition of CMV relative to the infants of seronegative mothers. The constancy of the odds ratios across the four time periods was assessed by the methods described by Breslow and Day.[8]

The life table method used here was only approximate because of slight variations in the time between visits and the assumption of constant risks within each time period.

## Results

Of the 246 mothers, 10 were black, four Asian, and six oriental, the rest being white. The mother's serological state for CMV was known for 246 of the 253 infants seen six weeks after birth. The remaining seven had booked elsewhere for their antenatal care, and information on their CMV state was not available. Of the 246 mothers whose CMV state was known, half were seropositive; this rate is similar to that among women attending the antenatal clinic at this hospital.

As a check on the reliability of using virus isolation to define infection blood samples taken at 1 year of age were analysed for antibody to CMV. Antibodies were present in 45 of the 46 children who had excreted virus in their urine, and no additional children with antibodies from whom CMV had not been isolated were identified. The one seronegative child from whom virus had been isolated was first excreting CMV at 1 year, and seroconversion may not yet have occurred.

Table 1 shows the number of children excreting CMV at each age studied. The earliest positive urine cultures were obtained between 3 and 4 weeks. By one year 46 infants (20% of those sampled at this age) were excreting virus. The chances of acquiring

Table 1 *Acquisition of cytomegalovirus infection*

| | *Age at screening* | | | |
|---|---|---|---|---|
| | *6 Weeks* | *3 Months* | *8 Months* | *1 Year* |
| No screened | 253 | 249 | 247 | 234 |
| No (%) excreting CMV | 9 (3·6) | 30 (12·0) | 37 (15·0) | 46 (19·7) |

CMV infection, however, were far from uniform and depended on maternal characteristics (Table 2). The risk of acquiring CMV was much higher for children of seropositive mothers than for children of seronegative mothers. Breast feeding was also strongly related to acquisition of CMV. The mother's age and social class, however, showed no relation to the acquisition of infection. There was no important difference in the proportions of infants from the special care baby unit and postnatal wards who had acquired infection.

Only five of the 123 infants born to seronegative mothers became infected, and two of these had received seropositive blood while in the special care baby unit. One, who had been born at 40 weeks and weighed 3400 g, had been given 70 ml of seropositive blood on day 16 and was found to be shedding virus when 3 months old; urine samples taken up to six weeks had been negative. The other infant had been born at 26 weeks' gestation and weighed 650 g; he had received 12 ml of seropositive blood at birth, 10 ml when 2 weeks old, and 10 ml when 3 weeks old. Virus was first isolated from the urine at 8 weeks. Weekly urine samples up to then had been negative for CMV. The source of infection for the three other children of seronegative mothers, one of whom was first found to be shedding CMV at 8 months and two at 1 year, was unknown. None of the children had received day care. Interestingly, the mothers of the two children who first shed CMV when 1 year old were seropositive when they booked for subsequent pregnancies the following year. Maternal serological state was not otherwise monitored and could have changed over the one year period Assuming a 3% seroconversion rate in the seronegative groups,[9 10] we would expect to find three or four maternal seronconversions.

As the major factors identified to be associated with acquisition of CMV infection were breast feeding and mothers' serological state the subsequent analysis was confined to these two factors Figure 1 shows the rate of acquisition rate of CMV, defined as the number of new cases/1000/week. The rate was highest in the period between nine and 15 weeks.

Life table analysis showed that by one year 39% of infants of seropositive mothers who breast fed had become infected, compared with 24% of those who were bottle fed. Among the infants of seronegative mothers the percentages were 11% and 2% respectively. Infants with seropositive mothers had a far higher rate of infection than those with seronegative mothers, whether they were being breast fed (odds ratio 9·3, 95% confidence interval 3·6 to 24·0) or bottle fed (odds ratio 18·7, 95% confidence interval 4·3 to 80·0). The effect of maternal seropositivity on the aqusition of infection in breast fed infants tended to diminish over time ($\chi^2=7{\cdot}5$, df=1, $p<0{\cdot}01$).

Breast feeding was also associated with infection, though less strongly than the mother's seropositivity Among infants of seropositive mothers the odds ratio of acquisition of CMV in breast fed,

Table 2 *Factors associated with acquisition of CMV infection in first year*

| | *No at risk* | *No (%) of infants acquiring CMV* |
|---|---|---|
| *Mothers' serological state:* | | |
| Seropositive | 123 | 41 (33·3) |
| Seronegative | 123 | [illegible] (4·1) |
| Total | 246 | 46 (18·7) |
| | *Characteristics of seropositive mothers* | |
| *Social class* | | |
| Non-manual | 56 | 19 (33·9) |
| Manual | 65 | 20 (30·8) |
| Other | 2 | 2 (100·0) |
| *Hospital unit:* | | |
| Postnatal ward | 80 | 28 (35·0) |
| Special care baby unit | 43 | 13 (30·2) |
| *Maternal age (years)* | | |
| <20 | 5 | 2 (40·0) |
| 20–25 | 56 | 17 (30·4) |
| 30+ | 62 | 22 (35·5) |
| *Breast feeding* | | |
| Never | 36 | 7 (19·4) |
| <12 weeks | 23 | 7 (30·4) |
| 12 + weeks | 64 | 27 (42·2) |

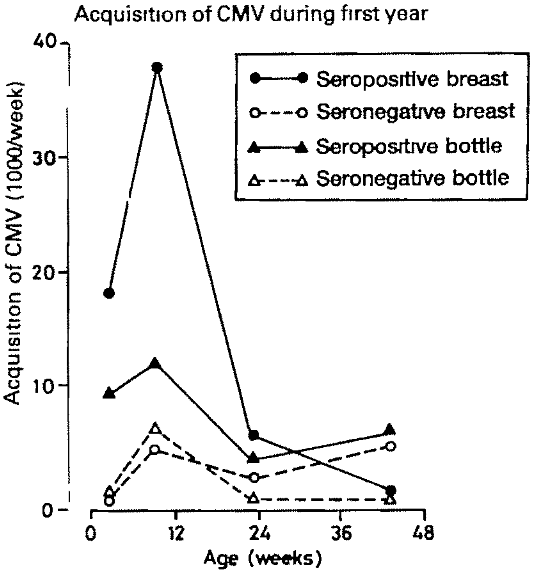
Acquisition of CMV during first year

Fig 1 *Acquisition rate of cytomegalovirus infection, by mother's serological state and method of feeding.*

compared with bottle fed, infants was 2·3 (95% confidence interval 1·1 to 4·9). There was a similar result in infants of seronegative mothers (odds ratio 4·7), but the confidence interval was wide (1·0 to 22·0).

**Source of maternal infection.** Isolation of CMV from breast milk was intermittent. CMV was isolated from colostrum or milk samples collected from 17 of 87 (20%) mothers who had breast fed. The infants of 13 of 17 (76%) mothers who shed virus in breast milk acquired infection. One mother who did not breast feed at all was shedding CMV in colostrum, and her infant acquired infection at 1 year of age. CMV infection was not acquired by breast fed infants of four mothers despite virus in breast milk or colostrum. This included the infant of one mother from whose breast milk the virus was repeatedly isolated.

CMV was isolated from the urine of three women (1·2%) in the first week after delivery. Two of these women were also shedding virus in their breast milk, and both their children acquired CMV infection.

Four pairs of CMV isolates, from mother's breast milk and their infant's urine, were typed for molecular relatedness by restriction endonuclease digestion analysis.[6] In three pairs of isolates the breast milk samples had similar DNA fragments to those isolated from their respective infants' urine, indicating that infection had occurred with the same strain of CMV. The fourth pair showed only minor differences in the patterns, which were quite distinct from the major differences seen between epidemiologically unrelated strains of CMV.

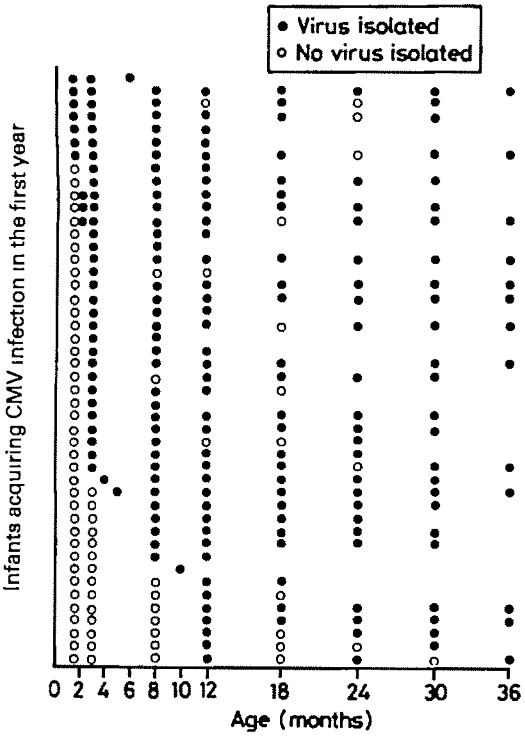

Fig. 2 *Duration of viral excretion in infants with acquired cytomegalovirus infection*

**Duration of viral shedding in infants with acquired CMV infection.** Further urine samples were obtained at 18, 24, 30, and 36 months from those children infected during the first year. Figure 2 shows that only one of 25 infants excreting at 12 months and followed up until 30 months was not shedding virus in the urine; this same infant was shedding virus at 36 months. All 13 infants from whom a urine sample was collected at 36 months were shedding CMV in their urine.

## Discussion

The prevalence of CMV infection acquired by children during the first year varies throughout the world, and in populations of different ethnic and social backgrounds it ranges from 8% to 60%[11] In our study one fifth of children had acquired CMV infection by 1 year of age and 12% were already infected by 3 months. Previous cross sectional studies in the United Kingdom of children in hospital showed lower rates of infection.[12] [13] In a study of unselected admissions to acute medical, surgical, and paediatric wards in one hospital in 1968 CMV was isolated from 2·5% of 118 neonates, 9% of 32 infants aged 2·5 months, and 10% of 104 children aged 6 months to 4 years.[12] In the collaborative study,[13] which was also cross sectional and based on hospital admissions, the prevalence of virus excretion was 1·8% in 508 infants aged under 3 months, 3·2% in 220 aged between 3 and 5 months, and 5·8% in 207 aged 6 to 11 months.

The overall rate of seropositivity in mothers is the most important factor determining the extent of early acquisition of CMV. In countries where a high proportion of women of childbearing age have antibodies to CMV the acquisition of early infection is high. In Finland in a population where 82% of women were seropositive, 32% of 148 infants acquired CMV infection during their first year.[14] Most of these infants were infected by 4 months, and few acquired infection after this age. None of the infants of the 23 seronegative mothers became infected, whereas 38% of those born to seropositive mothers acquired infection. These results are comparable with those in our study, in which 34% of infants of seropositive mothers were infected by 1 year, most by 3 months. In Japan high rates of excretion of CMV were also reported[15] in a population where the rate of seropositivity among women of childbearing age is over 90%.[16] In a longitudinal follow up of 100 healthy infants born at term in the United States of America, 3% of 77 neonates were excreting virus, and 11% of 73 infants at 3 months[17] The prevalence at 6 months was 13% of 82 children, and at 1 year 11% had antibodies indicating past infection. At the examination at 2–2½ years no new excretors of CMV were found among the 30 susceptible children.

It has been suggested that acquired infection is more common in children from the lower socioeconomic groups; this is likely to be reflected by seropositivity rates, but in our study there was no association with social class when the serological state of the mother had been allowed for.

The rapid acquisition of CMV infection in infants of seropositive mothers within the first three months of life, and the relative absence of infection among infants of seronegative mothers, indicates that the mother is the major source of infection. Infection may be acquired during delivery, through contact with infected cervical secretions, or after birth. Important sources of postnatal infection include breast milk,[11 18 19] and transfusion of seropositive blood products.[20–22]

Reactivation of latent CMV infection and virus shedding from the cervix is common,[23 24] and virus excretion may be enhanced during the immediate postpartum period.[25] There is poor correlation between cervical shedding during pregnancy and fetal infection, but the association between maternal shedding and transmission of infection to the offspring in early life is strong.[11] Reynolds *et al* reported the early acquisition of CMV infection in 40% of infants born to women from whom the virus had been isolated from the cervix in late pregnancy and concluded that CMV transmitted at the time of delivery was an important source of infection.[23] In a prospective study of 81 infants born to women known to be excreting CMV during pregnancy and in whom congenital CMV infection had been excluded, 21 (26%) had acquired infection by 1 year 75% of these infections had occurred by 14 weeks.[26] In our study we had no information about cervical shedding of CMV, and virus was grown from the urine of only 1·2% of women.

Infected breast milk is an even more efficient source of acquired infection. Hayes *et al* isolated CMV from milk or colostrum, or both, from 17 of 63 (27%) seropositive women.[18] Virus was isolated significantly more often after the first week than before Stagno *et al* reported the isolation of CMV at least once in breast milk or colostrum from 38 of 265 (14%) seropositive women 25/70 (36%) in breast milk and 20/244 (8%) in colostrum[11] In a population with a high prevalence of immunity among women of childbearing age transmission through breast milk is likely to be the major source of infection. Indeed, in the present study the acquisition of CMV among infants of seropositive mothers was significantly higher in the breast fed group than in the bottle fed group. Virus was isolated from the breast milk of 20% of seropositive mothers who breast fed. Surprisingly, however, despite the presence of CMV in breast milk four breast fed infants did not acquire CMV infection.

In a parallel study done in the same hospital, specimens of breast milk were taken from a random sample of 140 women seropositive for CMV in the first week after birth and from 137 women attending for their first postnatal examination at six weeks. Virus was isolated from 2·9% of the colostrum samples and 15·2% of the breast milk samples collected at six weeks. Virus excretion was not related to the mother's age, unlike the prevalence of virus shedding in urine and from the cervix, which diminishes with age.[27]

Although CMV infection acquired in the neonatal period has been temporarily associated with pneumonitis,[28] it is seldom symptomatic, and we confirmed this. CMV infections transmitted by blood transfusion to premature infants born to seronegative mothers or those whose serological state was unknown, however, have resulted in severe and even fatal disease[20 21] It has been recommended, therefore, that blood products given to premature infants should be screened for CMV. It is not known whether expressed milk given to premature infants of seronegative mothers, who are the ones at greatest risk, may also become a source of serious nosocomial infection. It has been recommended that fresh donor milk fed to premature infants should be appropriately processed to reduce infectivity,[29] but this may decrease the potential benefit of the milk.

CMV infection is chronic, with viral shedding persisting for years. Our finding that children who had been infected in their first year still had virus in their urine at three years is important. This implies that infection in young children in the community is widespread and that most of this infection has been acquired from the mother at an earlier age. As acquired infection is so common in early life it is not possible to distinguish congenital from acquired infection after the first three or four weeks of life, even when neurological symptoms compatible with congenital infection are present.

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# Maternal smoking during pregnancy and lower respiratory tract illness in early life

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SUMMARY In a national study of 12 743 children maternal, but not paternal, smoking was confirmed as having a significant influence on the reported incidence of bronchitis and admission to hospital for lower respiratory tract illness during the first five years of life. Reported rates of admissions to hospital for lower respiratory tract diseases were found to be as high in children born to mothers who stopped smoking during pregnancy as in those whose mothers smoked continuously both during and after pregnancy. Rates of admissions to hospital for lower respiratory tract diseases in children whose mothers started smoking only postnatally were no higher than in those whose mothers remained non-smokers. Postnatal smoking seemed to exert a significant influence on the reported incidence of bronchitis, but less than smoking during pregnancy.

These findings suggest that maternal smoking influences the incidence of respiratory illnesses in children mainly through a congenital effect, and only to a lesser extent through passive exposure after birth.

Parental smoking has been incriminated as having a major adverse influence on the respiratory health of young children.[1-6] Fergusson *et al* found that only maternal, and not paternal, smoking was influential.[5 6] They suggested that fathers who smoked have less contact than mothers with young children, and so there is less irritation of the child's lower respiratory tract from passively inhaled smoke of paternal origin. There are other possible explanations. Maternal cigarette smoking during pregnancy is a health hazard to unborn children, affecting birth weight and predisposing to abortion;[7-9] some studies have suggested that there is an increase in congenital abnormalities in children born to mothers who smoke.[10-13]

Smoking by the mother during pregnancy may cause a congenital predisposition in the child to subsequent respiratory illnesses. We investigated this possibility using data from a national birth cohort study.

## Subjects and methods

CHES (the Child Health and Education Study) is a continuing survey of children studied neonatally in the British Births Survey.[14 15] The cohort originally comprised all children born in the United Kingdom, including Northern Ireland, from 5 to 11 April 1970 inclusive. In 1975, 12 743 children of the 16 015 born in that week and living in England, Scotland, and Wales were traced (79·6%). Health visitors interviewed the mothers at home and gathered over 500 items of information about social background, family, and health, including whether the child had had any episodes of bronchitis during the first five years, and whether the child had been admitted to hospital with a lower respiratory tract illness (wheezing, bronchitis, bronchiolitis, or pneumonia) and at what age.

At the interview in 1970 information had been gathered about the mother's smoking habit in pregnancy, the average number of cigarettes smoked each day, the time of giving up smoking if the mother was a previous smoker (recorded as months before delivery), as well as the child's birth weight and any neonatal problems. At the five year interview information was collected about the reported number of cigarettes, if any, smoked by each parent and the duration of regular smoking by each parent since the child's birth.

To allow for factors that could influence both smoking and respiratory illnesses the following information collected at the five year interview was included in multivariate analyses: sibling ranking at five years, the health visitor's assessment of the home equipment (luxurious, high standard or average, low, very low standard), whether the child had been breast fed, the number of times the family had moved house in the child's first five years, and the social index[16]—that is a composite assessment of socioeconomic state including domestic crowding, parental education, tenure of accommodation, type of neighbourhood, and paternal occupation.

The social data obtained in 1970 were less extensive than those obtained in 1975. The following factors were assessed. social class and mother's age, marital state, and length of full time education. Preliminary analysis included two way tabulations and $\chi^2$ calculations; for multivariate analyses logistic analysis of multiway contingency tables[17] using the generalised linear interactive modelling statistical package GLIM[18] was used to allow assessment of individual factors after simultaneous adjustment for all other factors in the model.

Where there were missing data (never more than 5% and usually less than 2%) as complete a set as possible was used in the analysis. Thus the denominators used to obtain percentages in the tables exclude missing values.

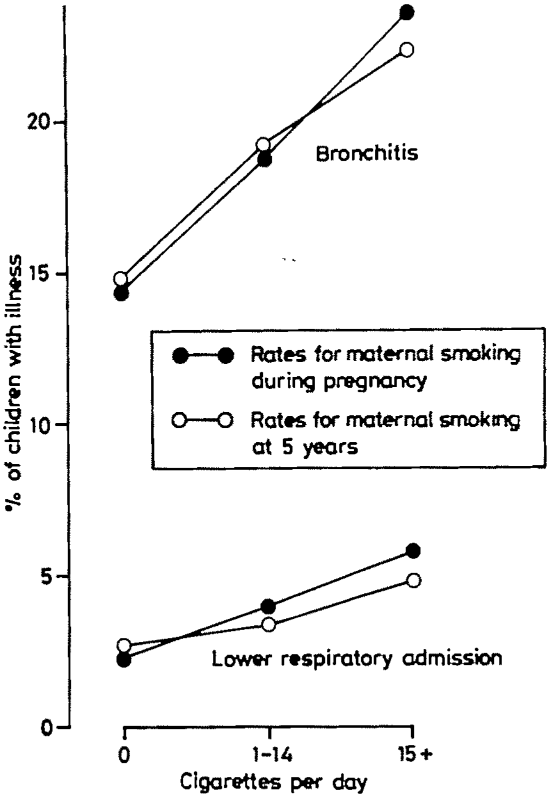

Figure *Comparative effect of increasing levels of maternal smoking during and after pregnancy on risk of bronchitis and admissions for lower respiratory tract disease in children aged 0–5.*

## Results

Initial cross tabulation showed that rates of lower respiratory tract illness in the children increased the more the mother smoked. This was so for smoking both during pregnancy and also subsequently (Figure) These dose response relations remained highly significant ($p<0{\cdot}001$) and were only slightly attenuated when allowance was made in multivariate analyses for the possible effects of birth weight, social index, home assessment, household moves, number of siblings, and breast feeding.

Tables 1 and 2 show the relations between respiratory illness in the children and parental smoking habits and confirms the findings of Fergusson *et al.*[5 6] Data collected at five years were used for this analysis as information on paternal smoking was not collected at the 1970 interview. In general, rates of admissions to hospital for lower respiratory tract illnesses and bronchitis followed the trend of the mother's smoking rather than the father's, with the highest rates occurring in children whose mothers smoked most heavily, irrespective of the father's cigarette usage. Logistic multiway contingency table analysis confirmed this relation.

Table 1 *Children aged 0–5 admitted to hospital with lower respiratory tract illness according to parental smoking habits*

| *Daily No of cigarettes smoked by father* | *Daily No of cigarettes smoked by mother* | | | | | |
|---|---|---|---|---|---|---|
| | *None* | | *1–14* | | *15 or more* | |
| | *No studied* | *% Admitted to hospital* | *No studied* | *% Admitted to hospital* | *No studied* | *% Admitted to hospital* |
| None | 5216 | 2·7 | 924 | 3·0 | 1096 | 5·3 |
| 1–14 | 804 | 2·9 | 473 | 3·8 | 299 | 8·4 |
| 15 or more | 1559 | 2·8 | 770 | 3·4 | 1586 | 4·5 |

Table 2 *Children aged 0–5 with at least one episode of bronchitis according to parental smoking habits*

| *Daily No of cigarettes smoked by father* | *Daily No of cigarettes smoked by mother* | | | | | |
|---|---|---|---|---|---|---|
| | *None* | | *1–14* | | *15 or more* | |
| | *No studied* | *% With episodes of bronchitis* | *No studied* | *% With episodes of bronchitis* | *No studied* | *% With episodes of bronchitis* |
| None | 5039 | 14 5 | 893 | 19 3 | 1049 | 20 9 |
| 1–14 | 774 | 14 0 | 459 | 14 4 | 286 | 27 3 |
| 15 or more | 1514 | 16 2 | 742 | 19 0 | 1520 | 22 4 |

Maternal smoking had a significant influence ($p<0·01$) on both admissions to hospital with lower respiratory tract illness and the incidence of bronchitis; paternal smoking had no significant influence on either condition when maternal smoking was taken into account.

There was an overall high collinearity between maternal smoking during pregnancy and postnatal maternal smoking assessed at five years over 90% of women who smoked in pregnancy were still smoking when their children were 5 years old. To assess whether smoking during pregnancy influenced children's subsequent respiratory health independently of postnatal smoking it was necessary to identify mothers who changed their smoking habits before or after the birth of the study child and compare rates of respiratory illness in their children with those of the ones whose mothers smoked continuously or not at all.

Table 3 shows the rates of bronchitis and admissions to hospital for lower respiratory tract illness according to the mothers' smoking habits. Smoking during pregnancy, but stopping before the child was born, was associated with an increased incidence of all lower respiratory tract illnesses, but smoking only after the birth of the child had no obvious effect on admissions to hospital though an apparent effect on the incidence of bronchitis. Logistic analysis of these data confirmed the highly significant effect of smoking during pregnancy on both rates of admission to hospital ($p<0·001$) and incidence of bronchitis ($p<0·01$); postnatal smoking alone had no effect on admissions to hospital and a marginal, though not significant, effect on the incidence of bronchitis.

Table 3 *Children aged 0–5 admitted to hospital with lower respiratory tract illness, or having bronchitis, according to mothers' smoking habits*

| | *No studied* | *% Admitted to hospital* | *% With episodes of bronchitis* |
|---|---|---|---|
| Smoked continuously | 5629 | 4 4 | 20 3 |
| Smoked only during pregnancy | 493 | 5 9 | 18 9 |
| Smoked only after child was born | 353 | 3 1 | 18 2 |
| Never smoked | 5852 | 2 3 | 14 1 |

Because the effect of maternal smoking on children's respiratory health is most obvious in early life,[6] and because our information about postnatal smoking was collected when the children were 5 years old, the effect of varying duration of postnatal smoking was examined. Rates of admissions to hospital were not influenced, with smoking during pregnancy remaining highly significant ($p<0·001$) and duration of postnatal smoking having no significant effect. Rates of bronchitis, however, were found to be highest in children whose mothers smoked both during pregnancy and for most or all of the time from birth to age 5. Significant and independent effects from both smoking during pregnancy ($p<0·001$) and postnatal smoking ($p<0·05$) were found on logistic analysis. More than 10% of the information on the duration of postnatal smoking was missing, however, so these results must be assessed with caution.

The mothers were compared for marital state, social class, length of full time education, and age at

Table 4 *Social data (1970 survey) of mothers according to their smoking habits*

| | *No studied* | *% In social classes 4 and 5* | *% Who left school aged <16* | *% Unmarried* | *% Aged under 20* |
|---|---|---|---|---|---|
| Smoked continuously | 5629 | 26 0* | 74 9* | 7 4 | 10 8 |
| Smoked only during pregnancy | 493 | 15 1 | 62 4 | 7 7 | 12 3 |
| Smoked only after child was born | 353 | 18 3 | 64 0 | 7 6 | 15 1 |
| Never smoked | 5852 | 18 5 | 58 4 | 3 0* | 6 5* |

*Significantly different from other values in column ($p<0·01$, partitioned $\chi^2$ analysis)

Table 5 *Percentage of children admitted with lower respiratory tract illness in different age groups according to mothers' smoking habits*

| *Age at admission (months)* | *Mother smoked during pregnancy (n=6122)* | *Mother did not smoke during pregnancy (n=6205)* | *p Value* | *Mother smoked when child 5 years old (n=5982)* | *Mother did not smoke when child 5 years old (n=6345)* | *p Value* |
|---|---|---|---|---|---|---|
| <12 | 2·07 | 0·93 | <0·001 | 2·09 | 0·95 | <0·001 |
| 12–35 | 1·83 | 1·05 | <0·001 | 1·76 | 1·13 | <0·01 |
| 35–59 | 1·14 | 0·68 | <0·01 | 1·05 | 0·77 | NS |

delivery (Table 4). Continuous smokers differed from non-smokers for each of these factors, but those who stopped smoking before birth and those who started smoking postnatally did not differ significantly from each other on partitioned $\chi^2$ analyses. Mothers who smoked continuously differed significantly from the other three groups in social class and educational attainment; non-smokers differed from the other three groups for marital state and age at child's birth. It seems unlikely, therefore, that variation in socioeconomic factors among the four smoking groups explains our results, nor did there seem to be an unexpected effect from paternal smoking: rates of illness in the children among the four groups did not vary significantly when patterns of paternal smoking were considered.

The age at which bronchitis occurred was not known, but the age at admission to hospital for lower respiratory conditions was. Table 5 shows the effect of maternal smoking habits on rates of hospital admission at different age periods during the first five years. Children with repeated admissions were counted only once during each age period. Maximum differences between admission rates for children of smoking and non-smoking mothers occured during the first year of life. There was, however, still a significant difference up to the age of 3 years, and this trend continued up to 5 years. Although there was high collinearity between the two assessments, smoking during pregnancy (those who smoked continuously and those who stopped during pregnancy) had a significantly more persistent effect than subsequent smoking (those who smoked continuously plus those who took up smoking after the birth)

## Discussion

These results, as well as confirming previous studies that have shown that parental smoking has a harmful effect on children's respiratory health,[1–6] suggest that smoking during pregnancy may have a more important and independent effect on the risk of lower respiratory illness in children than passive exposure to smoking after birth None of the previous studies on parental smoking and respiratory illness in children has considered a congenital effect from maternal smoking in pregnancy; because of the size and range of CHES, however, it has been possible to examine the effects of both smoking and changing smoking habits. With the application of log linear modelling techniques we were able to assess the prenatal and postnatal components of the overall effect of smoking on children's respiratory illness. In the light of these results earlier studies and their recommendations may require reappraisal.

Rates of admission to hospital for lower respiratory illnesses at least once during the first five years of life were as high in children whose mothers smoked at some time during pregnancy but who stopped before delivery and did not then smoke postnatally as in children whose mothers smoked in pregnancy and continued to smoke after the birth of the child. Rates of admission to hospital remained low when mothers who did not smoke during pregnancy began smoking subsequently. Smoking after birth did not influence rates of admission to hospital independently of smoking during pregnancy. As far as bronchitis during the first five years of life was concerned, smoking during pregnancy had a major effect, but postnatal smoking also seemed to influence rates of illness Although rates of bronchitis were higher in children of mothers who smoked only during pregnancy and not subsequently than in children whose mothers never smoked, the highest rate of bronchitis was seen in children whose mothers smoked both during pregnancy and during the children's first five years. The need for admission to hospital probably reflects more serious respiratory disease than does reported bronchitis.

The findings concerning the level of maternal smoking support our overall conclusions. Mothers who continued to smoke tended to smoke more with time. Only 30·4% of these mothers were heavy smokers (15 or more cigarettes a day) during pregnancy, whereas 50·5% were five years later Only 15·0% of those who stopped smoking had been heavy smokers, compared with 27·7% of those who started smoking postnatally Thus heavier postnatal smoking did not overcome the apparent harmful effect of smoking during pregnancy.

Rates of admission to hospital were highest in children of mothers who smoked during the first year of life (Table 5). Although there was a strong correlation between the two measures, smoking assessed during pregnancy seemed to have a more persistent effect than postnatal smoking assessed five years later.

These findings suggest that smoking during pregnancy may cause congenital damage to the developing respiratory system, either the bronchial tree or the developing lung vasculature, as has been shown in the umbilical vessels.[19] An alternative explanation for the apparent effect of smoking during pregnancy is that some interference with the immune system might predispose to respiratory infections—a secondary congenital immunodeficiency. Cigarette smoking is immunosuppressive both in vivo and in vitro.[20] Datau *et al* described abnormalities of polymorphonuclear leucocyte function in children of parents who smoke,[21] and Paganelli *et al* showed an abnormality in immune function in cord blood from mothers who smoke.[22]

Cigarette smoking during pregnancy has been associated with reduced birth weight, and low birth weight is associated with a wide range of defective immune functions that might predispose to respiratory infection.[23] Low birth weight, although showing a highly significant correlation with rates of both admission to hospital and bronchitis, had its effect independent of maternal smoking.

An additional observation concerns the rate of lower respiratory illness in the offspring of teenage mothers in our study population. These children for various social, environmental, and biological reasons might have been expected to have a high rate of lower respiratory tract illness; they were more likely than children born to older mothers to have low birth weights, to have unmarried mothers of low educational attainment and low social class, to live in poor neighbourhoods, to move frequently, and to have more siblings at the age of 5. Their mothers were more likely than older mothers to be smokers and to be heavy smokers (15 or more cigarettes a day) when the children were 5 years old. These children were, however no more liable than children of older mothers to bronchitis or to be admitted to hospital.[24] A possible explanation for these paradoxical results was the finding that although teenage mothers were more likely to smoke some cigarettes during pregnancy, they were less likely than older mothers to be heavy smokers during this time, especially those who were under 18 years old when their children were born. Rates of respiratory illness across the whole maternal age range in general followed rates of smoking during pregnancy and not postnatal smoking.[25]

Many of the data used in this study were collected retrospectively, and so variable maternal recall might have influenced the findings. The large sample size and representativeness of the study population, however, should reduce this effect. The data also reflected the current habits, and are consistent both for reported bronchitis and the more objective variable of admission to hospital. Adequate agreement was found between medical data and parental reports of lower respiratory tract illness resulting in consultations with general practitioners[2] and hospital admission,[26] even though there may be variation between the two sources in exactly what names the respiratory conditions are given.[27] The data used in the present analysis were collected in 1970 and 1975, before there was widespread appreciation of the possible ill effects of parental smoking on children's respiratory health; the questions are thus likely to have been honestly answered.

The accumulated evidence suggests that, whatever the mechanism, exposure to cigarette smoke is bad for children during both intrauterine and subsequent life.

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## Editorial Committee

Members of our Editorial Committee usually serve for five years. We thank Dr A S Hunter and Professor J S Wigglesworth, who have retired from the Committee, for their excellent work on behalf of the Journal

We welcome as new members Dr M J Dillon, Consultant Nephrologist, Hospital for Sick Children, London; Dr I M Hann, Consultant Haematologist, Royal Hospital for Sick Children, Glasgow; Dr J W Keeling, Consultant Pathologist, John Radcliffe Hospital, Oxford, and Dr J F N Taylor, Hospital for Sick Children, London.

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# Breast feeding increases concentrations of IgA in infants' urine

A PRENTICE

*Medical Research Council Dunn Nutrition Unit, Cambridge*

SUMMARY To investigate the influence of breast feeding on mucosal immunity the concentrations and daily outputs of IgA and lactoferrin in urine were measured in 10 breast fed and 12 infants fed on formula milk at 6 and 12 weeks of age. The concentrations and outputs of secretory IgA in urine were significantly higher in the breast fed group by a factor of three. The secretion of IgA in urine by the breast fed infants was characteristic of the baby and was not related to the intake of IgA from breast milk. Lactoferrin concentrations were similar in the two groups at both ages. In addition to secretory IgA, two thirds of all samples contained proteins with α chain but no secretory component antigenic determinants. Breast feeding seems to increase the local production of secretory IgA into the urinary tract during early childhood, thus providing enhanced protection from infection.

Epidemiological studies have shown that breast feeding confers a measure of protection against infection on an infant. The mechanisms entailed, however, are still not fully understood. There is some evidence that breast feeding enhances the mucosal defence system,[1 2] although the data are conflicting.[3 4] The purpose of this study was to quantitate two immune proteins IgA and lactoferrin in the urine of healthy infants fed exclusively on breast milk, or on formula milk with a cow's milk base to assess mucosal immunity at a site remote from the gastrointestinal tract.

## Patients and methods

Ten breast fed and 12 formula fed infants in the Cambridge area were studied. They were all born at term with a mean birth weight of 3400 g, and were all healthy with no history of urinary tract infections. Total collections of urine and faeces were made over seven day periods when they were 6 and 12 weeks old. The collections were made in the subject's home using preweighed disposable nappies which were frozen immediately. The study, which had the approval of the ethical committees of the Dunn Nutrition Unit and the Cambridge Area Health Authority, formed part of an investigation into the use of breast milk immune protein. Milk intakes were measured using the deuterium oxide dilution method, and samples of breast milk and formula milk were obtained daily for analysis. Nappies were also collected from five each of the breast fed and formula fed subjects at 26 weeks of age, once they had been introduced to solid foods. Full details of the subjects and methods, together with the results of the faecal and milk analyses, have been published.[5]

Unsoiled nappies were gently squeezed and the urine collected. Any nappy with traces of faecal material was regarded as soiled and rejected from the urine analysis. The urine specimens were pooled in proportion to the weight of urine contained in each nappy.

Samples were analysed for human total IgA, secretory IgA, and lactoferrin, using enzyme linked immunoabsorbent assays.[5] Standards used were purified human secretory IgA (Cappell) and human lactoferrin (Calbiochem-Behring). The total IgA assay detects any molecules containing α chain determinants—for example, secretory IgA, serum IgA, IgA fragments—while the secretory IgA assay is specific for molecules with determinants for both α chains and secretory component (secretory IgA). The two IgA assays give identical results when secretory IgA is the only IgA species present.[5] Other species which contain α chains but no secretory component, such as serum IgA and certain IgA degradation products, are detected only by the total IgA assay. Fragments of IgA that do not contain α chain determinants are not detected by these assay systems No degradation of secretory IgA or lactoferrin has been shown during the analytical procedures[5] The thresholds of detection are 30 µg/l for both the IgA assays and 2 µg/l for lactoferrin. Concentration of urine samples before analysis was unnecessary due to the high sensitivity of the assays.

Immune protein concentrations in urine were transformed to logarithms because of the skewed distribution of the data Concentrations below the detection limit were entered into calculations at the threshold value. Calculation of urinary outputs was based on the weight of urine collected, on the assumption that 1 ml of urine weighed 1 g. The weight of urine present in each soiled nappy was estimated as the average weight of urine in unsoiled nappies over the collection period Mean (+1 geometric standard error) values are given. Statistical methods used were Student's *t* test (for independent and dependent values as appropriate), linear regression, and analysis of variance.

## Results

The Table shows the concentrations of secretory IgA in urine which were significantly higher in the breast fed infants than in the formula fed group. The magnitude of the difference was threefold at both 6 and 12 weeks of age. The mean values (µg/l) were: at 6 weeks, breast fed=148, formula fed=44, $p<0\cdot01$; at 12 weeks, breast fed=237, formula fed=71, $p<0\cdot001$. Secretory IgA concentrations rose significantly between the time points in the formula fed group ($p<0\cdot05$), but not in the breast fed infants. At 6 weeks, two breast fed and seven formula fed infants had IgA concentrations below the detection limit. By 12 weeks all subjects had measurable IgA.

Measurements obtained using the total IgA assay exceeded secretory IgA values in 66% of samples. This showed the presence, in addition to secretory IgA, of molecular species containing α chain but no secretory component determinants. In several samples the concentration of total IgA (using secretory IgA as standard) was more than double that of secretory IgA. The nature of the molecular species entailed has yet to be elucidated. Total IgA concentrations in urine were significantly higher in those infants breast fed than in those formula fed ($p<0\cdot01$). This difference was due to the increased secretory IgA concentration, as the amounts of non-secretory IgA species were similar in the two groups. The ratio of total IgA to secretory IgA in samples of individual children rose between 6 and 12 weeks, showing an increased abundance of non-secretory IgA species; in the breast fed babies at 6 weeks it was 1·1 (0·1), and at 12 weeks 1·4 (0·1) $p<0\cdot02$; in the formula fed babies at 6 weeks it was 1·2 (0·1) and at 12 weeks it was 1·6 (0·2), $p<0\cdot05$. Consequently, the total IgA concentration also increased between the two ages ($p<0\cdot05$).

Lactoferrin concentrations in urine were not significantly different between the breast fed and formula fed infants and showed no change between the two ages. A wide range of concentrations was observed, the mean value recorded being 22 µg/l (12 µg/day). At 6 weeks, one breast fed and three formula fed infants had concentrations of lactoferrin

Table *Immune proteins in urine of infants either breast fed or formula fed*

| | *Breast fed at* | | *Formula fed at* | |
|---|---|---|---|---|
| | *6 weeks (n=10)* | *12 weeks (n=12)* | *6 weeks (n=10)* | *12 weeks (n=12)* |
| Secretory IgA | | | | |
| Concentration µg/l, mean (geometric SE) | 148 (66)† | 237 (69)‡ | 44 (7) | 71 (15)¶ |
| range | (30–760) | (80–790) | (30–110) | (30–180) |
| Output µg/day, mean (geometric SE) | 70 (22)* | 126 (36)‡ | 22 (4) | 39 (8)¶ |
| range | (15–440) | (42–417) | (15–77) | (15–104) |
| Total IgA | | | | |
| Concentration µg/l mean (geometric SE) | 159 (76)† | 322 (102)† | 49 (9) | 112 (35)¶ |
| range | (30–1070) | (105–1390) | (30–129) | (33–609) |
| Output µg/day, mean (geometric SE) | 84 (18)† | 172 (56)¶ | 25 (5) | 63 (18)‖ |
| range | (15–625) | (56–811) | (15–94) | (21–371) |
| Lactoferrin | | | | |
| Concentration µg/l, mean (geometric SE) | 30 (22) | 37 (20) | 12 (7) | 21 (13) |
| range | (2–542) | (6–266) | (2–130) | (2–849) |
| Output µg/day, mean (geometric SE) | 18 (12) | 19 (10) | 6 (3) | 12 (32) |
| range | (1–258) | (3–132) | (1–89) | (1–446) |
| Urine volume | | | | |
| L/day, mean (geometric SE) | 0·53 (0·02) | 0·53 (0·03) | 0·55 (0·04) | 0·58 (0·04) |
| range | (0·45–0·61) | (0·42–0·70) | (0·37–0·83) | (0·38–0·81) |

Significant differences for breast *v* formula fed infants at each age=*$p<0\cdot02$, †$p<0\cdot01$, ‡$p<0\cdot001$
Significant differences for breast *v* 12 week values in each group=¶$p<0\cdot05$, ‖$p<0\cdot01$

below the threshold of measurement. By 12 weeks all breast fed and 11 formula fed infants had detectable amounts.

The concentrations of secretory IgA and lactoferrin in urine samples were positively correlated within each group of children (breast fed p<0·01, formula fed p<0·05) No associations could be found in the breast fed infants between the concentrations of these urinary proteins and daily intakes of secretory IgA and lactoferrin from breast milk at either age

Estimated daily volumes of urine were similar in breast fed and formula fed children at both ages, with an average of 0·55 1/day. No association was found between urine volume and concentrations of immune protein in either group of infants. Consequently, the variations in daily output of urinary IgA and lactoferrin paralleled the concentrations.

The breast fed infants had characteristic concentrations of IgA and lactoferrin in urine at the two ages as judged by analysis of variance (p<0·01 for both proteins). No correlations existed between the total:secretory IgA ratio nor the IgA lactoferrin ratio in urine and in faeces of any child. These findings showed that the accidental contamination of urine with faecal material, which contains comparatively high amounts of these two proteins, was minimal.[5]

Between 12 and 26 weeks of age the concentration and daily output of secretory IgA increased in the small group of formula fed subjects on whom repeat studies were made (p<0·05), reaching mean (SEM) values of 134 (85) μg/l and 74 (47) μg/day, respectively, whereas the concentrations noted for the five breast fed infants were unchanged The ranking of individual breast fed infants according to the urinary secretory IgA concentrations was maintained until 26 weeks (p<0·02). Significant differences in secretory IgA concentrations could not be detected between the breast fed and formula fed infants at 26 weeks. Urinary volumes and lactoferrin concentrations remained unchanged and were similar in the two groups.

## Discussion

Secretory IgA and lactoferrin are antimicrobial proteins that form an important part of the mucosal defence system and are present in all human external secretions.[6] The results of this study show that breast feeding increases the concentration and daily production of secretory IgA in urine during the first three months of life

The daily intake of IgA from breast milk is about 1 g/day.[5] The increased concentrations of IgA in urine may represent the transfer of small quantities of maternal antibody from the infant's gut via the blood. This seems unlikely, however, because concentrations of lactoferrin in urine were not increased in the breast fed group despite the high concentrations of lactoferrin in breast milk. In addition, IgA concentrations in urine were not related to daily intake, and secretory IgA is a very large protein (molecular weight 375 000) that is unlikely to be filtered through the kidneys. A more likely explanation is that there are factors in breast milk which promote the local production of secretory IgA, possibly by the stimulation of IgA producing lymphocytes in the child's gastrointestinal tract which migrate to other mucosal sites. A similar mechanism has been proposed for the appearance in breast milk of IgA antibodies specific for antigens in the mother's gut.[7] In addition, breast milk has been shown to contain a factor that stimulates the differentiation of cord blood lymphocytes into IgA producing cells in vitro.[8]

Raised IgA concentrations in the saliva and nasopharyngeal secretions of breast fed infants have been noted during the first days of life,[1 2] although other authors have failed to detect them.[3] These studies have shown that the differences either become negligible[2] or reverse[4] as the child becomes older The reason may be that local antibody production in formula fed infants is stimulated by exposure to ingested material. The study presented here showed long term differences between healthy breast fed and formula fed infants in the concentrations of secretory IgA measured in a fluid distant from the gastrointestinal tract. The observations that the concentration of secretory IgA remained consistently raised in the urine of individual breast fed infants between 6 and 12 weeks of age at a time when the concentration was increasing in formula fed infants, and that by 26 weeks of age IgA concentrations in the formula fed group had approached those in the breast fed group, suggest that breast feeding promotes the maturation of local antibody production in the first weeks of life.

The mean output of lactoferrin recorded in the present study for healthy infants born at term was 12 μg/day. No differences were detected between the breast fed and formula fed groups. A recent study has shown that very low birthweight babies fed on a formula based on human milk excreted grossly increased amounts of lactoferrin compared with formula fed babies (1140 μg/day *v* 15 μg/day).[9] It seems likely that these very high values were a reflection of the prematurity of the subjects.

The production of IgA in urine is low at birth and increases with age [10] The daily outputs of IgA from urine recorded in the Cambridge infants were within normal limits reported for children[10] but were about one tenth of adult values.[11] Several studies have shown that low concentrations of IgA in secretions from the urinary tract,[12 13] vagina,[14 15] nose,[16] and breast[17] are associated with an increased susceptibility to mucosal infections. It would seem likely, therefore, that the threefold increase of IgA in the urine of breast fed infants at 6 and 12 weeks of age enhances mucosal immunity during the vulnerable first months of life.

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# Measurement of milk intake by deuterium dilution

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SUMMARY In 14 studies, each lasting seven days, on eight bottle fed infants milk intake was measured by deuterium dilution and by weighing the formula consumed and oral losses. Mean (SD) milk intake was 829 (108) g/day when measured by isotope dilution and 837 (98) g/day when measured by direct weighing, giving a mean difference between methods of 1·0 (5·0)%. Thus the stable isotope procedure is a potentially useful method for investigating lactation and nutritional problems.

Measurement of milk intake is fundamental to scientific, epidemiological, and clinical research on infant nutrition. Deuterium oxide ($^2H_2O$), given orally to mother or infant, has been used by some workers to estimate the intake of breast milk.[1–3] Unlike alternative methods, such as test weighing[4] or determination by flow meter,[5] the stable isotope procedure does not need an observer or apparatus to be present at the time of feeding. This method is supported by sound theoretical arguments,[6] by the consistency of data obtained in this way compared with data obtained by conventional test weighing,[7] and by studies in animals.[3 9] There is little information, however, on the validation of stable isotope methods in infants.[4 10] We investigated the validity of the 'dose to the baby' deuterium dilution method, giving the isotope to infants living at home and being bottle fed, whose intake could be accurately measured.

## Patients and methods

In 14 studies on eight healthy full term infants being bottle fed at 5 to 11 weeks of age milk intake was measured by deuterium kinetics and the results compared with those obtained by weighing the intake of formula feed and oral losses directly. The methods were conducted simultaneously over seven day periods in the infants' homes. Approval was obtained from the ethics committees of the local hospital and Dunn Nutrition Unit.

Accurate data on formula intake were obtained by issuing preweighed bottles of ready to feed formula and weighing the bottles and residual milk contained in them after seven days. Oral spillages and regurgitations were measured by collecting them on preweighed absorbent tissues. Infants with a history of posseting were not included in the study. Small quantities of extra fluids given orally were weighed carefully and accounted for.

Details of the isotope method and the calculations used have been reported elsewhere,[11] but the principal steps were as follows. Two samples of urine or saliva were obtained from each infant before the study to determine natural concentrations of deuterium ($^2H$) in a body fluid. A weighed dose of sterile isotope solution providing about 0·1 g $^2H_2O$/kg body water was then given orally under careful supervision to ensure that the whole dose was taken. Samples of the same body fluid (urine or saliva) were collected at four and five hours and then daily for seven days, a period that covered two to three biological half lives of the isotope.

Water output was calculated from the rate of disappearance of deuterium from the body multiplied by its average dilution space[9] and adjusting for fractionation of deuterium in water vapour. Using the results of water balance studies on the same infants (unpublished data), we took a figure of 13% of water intake as being subject to fractionation (that is, evaporative loss)

Total water intake was calculated as water output plus water stored during growth. Water stored during growth was derived from the difference between the measured deuterium space at the start of the study and that estimated at the end.[11] Oral water intake was derived from total water intake minus insensible water intake through lungs and skin (5·7% of the total, as estimated previously).[11]

Milk intake was calculated from oral water intake, adjusting for any extra water consumed, the known water content of the formula, water derived from oxidation of milk macronutrients,[11] and water stored in fat and protein (calculated from body water and weight change and published values for the protein and water contents of lean body mass).[12] Calculations indicate, however, that there is no loss of accuracy in the general equation: milk intake= water intake/0·95.

This isotope method has potential sources of error. The calculation of water output depends on the assumption that the average loss of water subject to fractionation (estimated at 13%) applies to each infant. Nevertheless, a 100% error in this figure would result in only a 1% error in water output. The estimation of water intake from water output is subject to error in the measurement of water deposited during growth, though this can be derived precisely by this technique A fixed assumption, based on average data, is used to estimate insensible water intake, yet in individual infants variations may occur according to minute volume and ambient humidity

In six subjects a study comparing the two methods was performed on two separate occasions. For the purposes of analysis these studies were treated as independent: firstly, they were separated in time by six weeks, after major changes in body weight, body water, and milk intake had occurred, and, secondly, statistical analysis showed that within subject variation was closely similar to between subject variation when the methods were compared.

## Results

The mean (SD) weight of formula offered to each infant was 841 (100) g/day, and the weight of measured spills and regurgitations was within the range of 1–12 g/day. The Table shows the resultant mean weight of formula ingested weight together with individual values These data are compared with those derived by the isotope method. The mean values for milk intake determined by the two methods, 837 (98) g/day by weighing and 829 (108) g/day by isotope, were not significantly different by the paired *t* test ($t = 0{\cdot}748$). The correlation coefficient for the two sets of results was 0·93 ($p < 0{\cdot}001$). The mean difference (bias) between the methods (deuterium dilution minus weighed intake) was − 1·0%. The standard deviation of this difference was 5·0%, and thus the limits of agreement of the two methods (as defined by Bland and Altman)[13] were − 11% to + 9% (mean difference ± 2SD of difference). The highest individual difference in this study was 9·9%. The Table shows the results of estimates of total body water determined simultaneously by deuterium dilution.

Table *Comparison of milk formula intake by direct weighing and by deuterium dilution*

| *Total body water (% of body weight)* | *Milk intake (g)* | | *Difference (%)* |
|---|---|---|---|
| | *Weighed* | *By deuterium dilution* | |
| 70·9 | 993 | 987 | −0·6 |
| 63·1 | 975 | 1021 | 4·7 |
| 72·7 | 733 | 704 | −4·0 |
| 67·1 | 840 | 859 | 2·3 |
| 66·8 | 743 | 739 | −0·5 |
| 65·0 | 879 | 931 | 5·9 |
| 65·2 | 964 | 868 | −9·9 |
| 69·6 | 841 | 863 | 2·6 |
| 69·9 | 686 | 628 | −8·5 |
| 73·3 | 778 | 820 | 5·4 |
| 70·6 | 777 | 758 | −2·5 |
| 60·1 | 828 | 794 | −4·1 |
| 64·5 | 924 | 870 | −5·8 |
| 65·4 | 758 | 764 | 0·8 |
| Mean (SD) | 837 (98) | 829 (108) | −1·0 |

## Discussion

All methods of measuring milk intake are subject to error, and there is no standard against which a new procedure may be validated.[6] Test weighing has been used as a standard, but small errors on weighing may accumulate if an infant feeds frequently; water losses by evaporation result in weight loss during the feed, and food regurgitated outside the test weighing period will be included as intake. In this study we attempted to avoid some of these difficulties by weighing the intake of the formula directly We also carefully accounted for oral spills and regurgitations. Milk intake measured by deuterium dilution gave mean values that differed by only 1% from those obtained by our reference method.

The results of our study show that 95% of estimations made by the deuterium method could be expected to fall within the range of − 11% to + 9% of the weighed intake. Bland and Altman suggested a method for calculating the precision of the estimated mean difference between methods and the corresponding confidence interval.[13] Using this approach for our sample size of 14 paired observations, the 95% confidence interval for placing the mean difference between methods (deuterium method − 1% compared with weighed intake) would be − 3·9% to + 2·9%. The value of the deuterium method for work on individual subjects, as opposed to populations, for which the method is clearly valid, depends on the acceptable error for a particular study. We suggest that this method is suitable for most clinical and many laboratory investigations in individual patients, but we emphasise that all methods of measuring food or milk intake are liable to significant errors.

Further confirmation of the validity of our method comes from our previous study comparing water intake by isotope dilution and a conventional balance technique in four premature babies.[11] In contrast, Butte *et al* found that milk intake measured by test weighing gave a significantly different result from that determined by isotope, with unacceptable differences between methods of up to 65% in individual comparisons.[4] That study may have deterred other investigators from using the isotope method, and the differences between their findings and ours require explanation. Our choice of a reference method other than test weighing probably played a key part in the difference. Moreover, we adjusted the weighed intakes for oral losses of milk, though we were careful not to select babies with a history of possetting; oral losses in our study were never above 2% of intake. We suggest that a further explanation of the differences between the studies is that we chose periods of seven days for both methods whereas Butte *et al* test weighed infants for only 48 hours and used the isotope procedure either over those two days or for three or five days, thus extending beyond the test weighing period. Though Butte *et al* studied breast fed infants and we used formula intake as our reference method, we do not believe that this accounts for all the differences observed. Indeed, the less frequent feeding of many formula fed babies may disturb the linear decline in deuterium enrichment by phasic changes in water turnover; theoretically this should make the isotope method more precise in breast fed infants. More recently Vio *et al* found good agreement between direct weighing and isotope determination of formula intake, but their study was not conclusive because of a technical problem with the isotope procedure that suggested oral loss of the deuterium dose; total body water values of up to 196% of body weight were obtained.[10]

Test weighing is likely to remain a valuable method of measurement in nutritional studies. As facilities for deuterium estimation become more widely available, however, we suggest that use of the deuterium dilution method will increase. The choice between giving the dose to the baby (as studied here) or to the mother will depend on the particular study. Giving the dose to the baby is more direct, is cheaper (in that it requires analysis of fewer samples), provides additional important information on total body water, and is the only method using deuterium that is suitable for objectively measuring milk intake in formula fed infants. The procedure is non-invasive and requires only a small oral dose of labelled water (which is not radioactive) and daily sampling of saliva or urine; these can often be undertaken by parents without the intrusion of an investigator into the home. Deuterium dilution is the method of choice when the infant breast feeds frequently.[6] The relatively long study period minimises error due to daily variation in intake. Apart from its research applications, we foresee a role for this technique in clinical practice for outpatient investigation of infants for whom data on milk intake may influence diagnosis or management. Such investigation would also avoid the discouraging effect that test weighing has on some mothers whose milk production is marginal.

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## Commentary

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Lucas *et al* have compared the measurement of formula intake by the deuterium dilution technique and by weighing formula bottles over a seven day period and have shown close agreement between the two methods.[1] They refer to our paper in which we concluded that the deuterium dilution technique overestimates milk intake,[2] and this requires some elaboration.

Our trial attempting to validate the method was designed according to the original protocol reported by Coward *et al* [3] Differences in the way in which we used the method compared with that of Lucas *et al* require critical evaluation The equilibration period of two hours that we used to calculate total body water was insufficient, in experiment 2, however, values of total body water predicted from samples taken two hours after the dose of isotope had been given were only 2·7% higher than those obtained by extrapolation from the exponential curve of decay of the isotope to the time of the start of the experiment. Because the half life of water in infants is about three days, assessment of milk intake by the deuterium dilution technique over 48 hours is probably too short, although agreement between methods was not improved when we extended the experiment to 120 hours. Deuterium enrichment analysis was performed at the Dunn Laboratory in both our study and theirs. In our study it was done on a Micromass 602 D spectrometer and an Aqua-sira mass spectrometer; possibly better precision and accuracy were achieved by Lucas *et al* in their study.

The short duration (48 hours) of the test weighing session was an important limitation of our study. We now know that the estimate resulting from a 48 hour test weighing session should be within about 28% (95% confidence interval) of an individual infant's intake.[4] Although this shortcoming led to a less precise estimate, it would not result in a systematic overestimation

The way in which we calculated milk intake from the results obtained with the deuterium dilution technique was different from that used by Lucas *et al;* we made no adjustments for the fractionation of deuterium in water vapour. Lucas *et al* assumed that an equivalent of 13% of water intake was subject to fractionation. Although this proportion seems low, they are correct in stating that a 100% error in this figure would result in about a 1% error in water output. More importantly, they incorportated a correction factor of 5·7% and assumed this to be insensible water intake This value was derived from a previous experiment with preterm infants and was the difference in intake observed between weighed records and results obtained by deuterium dilution. Although it may encompass insensible water influx, it also includes other possible sources of error.

Water influx through the skin and respiratory passages may be a potential, uncontrollable source of error in the 'dose to the infant' version of the deuterium dilution technique The input of water vapour through the skin should be proportional to ambient humidity and the permeability of the skin to water.[5] Influx through the lungs should be related to respiratory minute volume and ambient humidity. If ambient water is depleted compared with the body's enrichment, water flux will be overestimated The effects of unlabelled ambient water vapour at various relative humidities on water influxes measured using tritium were shown in kangaroo rats.[5] With absolute humidities ranging from 3·8 to 19·8 mg $H_2O$/1 air water fluxes were overestimated by 7·7 to 44·2%, respectively. To account for this source of error variations in ambient humidity, skin permeability, surface volume ratio, and minute volume would have to be considered in the calculation of water flux. Application of a constant correction factor may not be appropriate in environments where humidity varies daily, and the differences between indoor air conditioned and outdoor settings must be taken into account, as would be the case in Houston, Texas, where our own studies were conducted.

Recent preliminary findings from our laboratory, however, suggest that water influx may present only a minor source of error in the 'dose to the infant' deuterium dilution method. We have found that formula intakes predicted from deuterium dilution were only slightly higher than values obtained from direct weighing of formula bottles. Milk intakes of breast fed infants were consistently overestimated by the deuterium dilution technique when compared with values obtained by five day test weighings to the order of 10% more than were formula intakes. Because there is no obvious reason for the difference in water flux dynamics of breast fed and formula fed infants we must evaluate the test weighing procedure critically. Our measurements of human milk intake were not corrected for insensible evaporative losses during feeding. We approximated, and possibly underestimated, the mean (SD) loss to be 3·0 (2·0)% of intake.[2] There is also the possibility that mothers did not weigh their infants at every feed. Although the diligence of these women and the consistency of milk intakes reported from several laboratories would suggest otherwise, we recognise it as a potential source of error. We find it even more perplexing that when we compared the 'dose to the mother' version of the deuterium dilution technique[6] and the test weighing method[7] we obtained good agreement.

At the time of writing we agree that the 'dose to the infant' version of the deuterium dilution technique is a promising method for measuring milk intake. The magnitude of the error due to water influx, however, requires further study, and the discrepancy in the extent of overestimation of milk intake seen between breast fed and formula fed infants requires explanation.

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# Fluctuating dystonia responsive to levodopa

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SUMMARY Four cases of hereditary progressive dystonia with diurnal fluctuation were studied. All were sporadic; three of them mimicked spastic diplegia; and the fourth showed some similarity to torsion dystonia. Emotional or cognitive disturbance, or both, was seen in three. The correct diagnosis was suggested by fluctuating signs and symptoms, which worsened towards evening, but this was reached only after many years of handicap, hospital admissions, and invasive diagnostic procedures. Typically there was a prompt, pronounced, and sustained response to moderate doses of levodopa. Sleep recordings were obtained in three patients and showed increased body movements during rapid eye movement sleep. Several close relatives had periods of increased leg movements during sleep It is suggested that hereditary dystonia responsive to levodopa should be considered as the diagnosis in children with fluctuating signs of motor disability syndromes, simulating torsion dystonia or spastic diplegia. Polysomnographic studies may be helpful in diagnosis and may also detect early or subclinical cases.

Chronic dystonia in childhood has traditionally been regarded as an incurable and progressive disease Over the past 15 years some cases have responded to treatment with modest doses of levodopa. Most of these were characterised by definite diurnal fluctuation of symptoms. Twenty five such cases have been described;[1–6] an additional 11 cases lacking diurnal variation have also been reported.[5 7 8] Because this disease or group of diseases presents in childhood and responds to treatment paediatricians should be aware of it.

We report four patients and discuss common diagnostic pitfalls and the use of polysomnographic studies in diagnosis.

**Case 1:** A girl began to stumble and fall at the age of 4. Walking became progressively more difficult and she tired easily. Bad school work and emotional difficulties led to ineffective psychotherapy and a transfer to a class for slow learners. From the age of 7, obesity, slack facies, and slow reactions and speech were noted; her sleep cycle was disturbed with waking before dawn and going to bed in the late afternoon. She had several episodes during which she could not walk and resorted to crawling. During these episodes, each of which lasted several hours, her head, arms, and fingers were flexed, her legs were extended, and her left foot assumed an equinovarus position.

Between the ages of 6 and 9 she was seen by various physicians who found different signs at different times—for example, normal and increased muscle tone; positive, equivocal, and absent Babinski signs; ankle clonus; and wide based gait with slow rigid movements most of the time

Investigations in five centres included electroencephalography, pneumoencephalography, air myelography; visual evoked potentials; nerve conduction velocity; electrocardiography; muscle biopsy, estimation of the activity in serum of creatine kinase and other muscle enzymes, thyroxine, ceruloplasmin, lactate and pyruvate (at rest and during ischemic effort); tensilon test; and electromyography at rest and on repetitive supramaximal nerve stimulation. All were within normal limits, except for the finding of a large fourth ventricle on pneumoencephalography, and the presence of type 2 fibre atrophy on histological examination of the muscle biopsy specimen. Tentative diagnoses included spastic diplegia, spinocerebellar degeneration, metabolic myopathy, and dystonia musculorum deformans

Examination at the age of 9 showed obesity (weight 42 kg, height 126 cm) with dull facial expression, coarse features, protruding tongue, drooling, and an occasional inappropriate transverse smile. She was alert and oriented, but only partly cooperative, with a short attention span and obvious distractibility. Her speech was monotonous and slurred. She stood on a wide base with her head slumped forward. Her gait was awkward, and characterised by short steps, toe walking, and abrupt stopping. The right arm tended to assume a wing position. These abnormal findings were least noticeable in the early morning and extremely striking in the late afternoon

Treatment with levodopa resulted in a prompt diminution of motor handicap, loss of weight, increase in alertness, and return of a normal sleep cycle. The abnormalities of facial appearance, gait, and posture disappeared, with the exception of mild residual clumsiness and minimal residual dystonic signs. When last seen her weight was normal for her age after a loss of 20 kg during the first few months of treatment. At the time of writing, she is now doing well in a normal school class and leading a normal social life with no motor disability. She has been maintained for seven years on 100 mg levodopa and 10 mg carbidopa (Sinemet, Merck) daily, without deterioration or side effects. She discontinued the drug herself on several occasions and this resulted in immediate reappearance of dystonic equinovarus posturing of the legs

**Case 2.** A young girl had been slightly clumsy since infancy. Her disability worsened at age 6 with progressive bradykinesia, tiredness, dystonic leg posturing, kyphoscoliosis, and leg twitching. By the age of 13 she needed help in the afternoons to get up from a chair and walk 20 metres The diurnal fluctuation of her symptoms was noted and the diagnosis was established at the age of 13½ She responded within an hour to a single test dose of 250 mg levodopa. At the time of writing she had been asymptomatic for six years on 250 mg levodopa and 25 mg carbidopa daily.

**Case 3.** A 12 year old girl developed progressive bilateral equinovarus, spastic paraparesis and scoliosis, and was confined to a wheelchair by the age of 13½. She had bilateral hand tremor from the age of 15, when additional findings included slowing of the basic electroencephalographic rhythm, impairment of spatial orientation on neuropsychological testing, bilateral ankle clonus, spasticity of leg adductors and flexors nystagmus on right lateral gaze, and hypomimia. The diurnal fluctuation of her symptoms was noted and the diagnosis suggested at the age of 15½. She responded well to levodopa within 24 hours At the time of writing she had been symptom free for two years of daily treatment with 375 mg levodopa and 37·5 mg carbidopa. Electroencephalogram and neuropsychological state reverted to normal.

**Case 4.** A 5 year old girl developed a progressive tendency to fall, particularly in the afternoons, clumsy gait, inturning of both legs, torticollis, scoliosis, and behavioural disturbances. By the age of 9 she could walk only five or six steps at a time during the afternoon, and showed torticollis, truncal torsion, leg inturning, bilateral intention tremors, mild bradykinesia, depressed affect, mutism, and negativism Psychotherapy did not help. The diurnal fluctuation of her symptoms was obvious from the outset, but the diagnosis was first suggested at the age of 9. Her neurological disability responded within 48 hours to levodopa. Her behaviour became normal within a month and psychotherapy was stopped. She was still asymptomatic after two years of receiving 125 mg levodopa and 12·5 mg carbidopa daily.

## Diagnoses

Onset of symptoms in our patients varied from 4 to 12 years The correct diagnosis was made three to eight years later. All four were girls and none had affected relatives. Parental consanguinity was noted in case 3. They all had the distinctive diurnal variation of disability and dystonic signs, with striking improvement after sleep. All four patients underwent numerous investigations in major medical centres. Table 1 lists the previous diagnoses considered and the various major diagnostic and therapeutic procedures, many of them invasive Results of all tests were within normal limits, except for the non-specific pneumoencephalography and muscle biopsy histology mentioned in case 1.

The eventual diagnosis was suspected on clinical findings alone These included various pyramidal signs in three of the four patients and disturbances of higher function, in addition to the main features of fluctuating dystonia, accompanied in all four cases by other signs of basal ganglia dysfunction. Table 2 lists these findings. One patient was confined to a wheelchair for two years before diagnosis, while the other three were handicapped but still partially ambulant. Three had been referred to rehabilitation centres with the diagnosis of chronic, incurable motor handicap.

Complete and repeated polysomnographic studies were performed on two consecutive nights in three of the patients, and in 11 unaffected immediate relatives. In all three patients increased body movements occurred during rapid eye movement

Table 1 *Previous diagnoses, investigations, and treatment in four dystonic patients*

| | *Case No* | | | |
|---|---|---|---|---|
| | *1* | *2* | *3* | *4* |
| Suggested diagnoses | | | | |
| Spastic diplegia | yes | yes | yes | no |
| Spinocerebellar degeneration | yes | yes | yes | no |
| Metabolic myopathy | yes | no | no | no |
| Torsion dystonia | yes | no | no | yes |
| Primary lateral sclerosis | no | no | yes | no |
| Huntington's chorea | no | no | no | yes |
| Wilson's syndrome | no | no | no | yes |
| Psychogenic tics | no | no | no | yes |
| Investigations and treatment | | | | |
| Pneumoencephalography or computed tomography | yes | yes | yes | yes |
| Myelography | yes | * | yes | yes |
| Electromyography | yes | yes | yes | yes |
| Muscle biopsy | yes | no | no | no |
| Femoral angiography | no | yes | no | no |
| Psychotherapy | yes | no | no | yes |
| Tenotomy | no | * | no | no |

*Recommended but not carried out

Table 2 *Clinical findings in four patients with fluctuating dystonia*

| | *Case No* | | | |
|---|---|---|---|---|
| | *1* | *2* | *3* | *4* |
| Pyramidal motor signs | | | | |
| Spastic paraparesis | yes | yes | yes | no |
| Ankle clonus | yes | no | yes | no |
| Hyper-reflexia | yes | no | yes | no |
| Hip flexor contractures | no | yes | no | no |
| Babinski signs | yes | no | no | no |
| Non-pyramidal motor signs | | | | |
| Fluctuating dystonia | yes | yes | yes | yes |
| Bradykinesia | yes | yes | yes | yes |
| Tremor, chorea mask face | yes | yes | yes | yes |
| Torticollis | no | no | no | yes |
| Higher functions | | | | |
| Emotional disturbance | yes | no | no | yes |
| Impaired spatial orientation | no | no | yes | no |
| Failure to learn | yes | no | no | no |
| Other findings | | | | |
| Scoliosis | no | yes | yes | yes |
| Pes cavus | no | yes | no | no |
| Sleep disorder | yes | yes | no | no |
| Drooling, slurred speech | yes | no | no | no |

(REM) sleep, mixed with numerous awakenings, but without obvious impairment of sleep structure. In two patients studies were performed both before and during treatment with levodopa. No noticeable decrease in body movements resulted from the treatment, although the sleep cycle abnormality disappeared. Among 11 relatives, all three fathers and two of the three mothers showed definite periods of leg movement during stage 2 sleep; a paternal grandfather and two of four siblings were similarly affected.

The effect of levodopa on these patients was prompt, effective, and sustained. All responded fully within 24–96 hours of starting treatment and all now function normally. Examination at the time of writing showed none of the patients had the previously apparent pyramidal signs nor disturbances of higher mental functions. Daily doses ranged from 375 mg (levodopa) and 37·5 mg (carbidopa) to 100 mg and 10 mg, respectively. Treatment has been continued for two to seven years without side effects or need for a change in dose.

## Discussion

'Childhood onset levodopa responsive dystonia' was first described by Segawa *et al* in 1971,[1] and nine cases from the same clinic were reviewed in detail five years later.[2] The syndrome was named 'hereditary progressive dystonia with marked diurnal fluctuation'. All cases responded promptly to levodopa Six of the nine cases were familial, with a pattern that suggested autosomal dominant inheritance with low penetration. An additional 16 cases have been reported since [3–6] Our cases fit the described pattern of childhood dystonia with pronounced diurnal variation; this is sufficient for diagnosis and predicting a good response to levodopa. Eleven other cases of chronic dystonia which responded to levodopa have been reported; in these diurnal fluctuation was absent.[5 7 8] Three families have also been reported to have cases both with and without diurnal fluctuation.[5] This implies that there is no genetic distinction between cases with and without diurnal fluctuation and that this striking and useful finding is not invariably present It is uncertain, however, whether all families with this syndrome share the same autosomal dominant genes. Our four sporadic cases, including one with parental consanguinity, suggest the possibility of a recessive phenocopy

None of the cases reported has shown an addiction to levodopa, even after 12 years of treatment.[2–8]

Homovanillic acid concentrations in the cerebrospinal fluid were studied in three patients.[3 7] These were low before treatment, and increased immediately after the levodopa was started. One of the three patients did not have diurnal fluctuation;[7] the authors suggest that concentration of homovanillic acid in the cerebrospinal fluid may be of use in predicting response to treatment with levodopa

Several other patients have been reported who may or may not have this syndrome These include two brothers with dystonia, without diurnal variation, and with a less than complete response to medication,[9] and two unrelated children with immediate response to levodopa, but with neither dystonia nor diurnal fluctuation [10] In addition, at least 18 cases have been reported in Japan of early onset Parkinsonism, usually familial, who showed both pronounced diurnal fluctuation and an unusually good response to chemotherapy.[11-12] These reports suggest that chronic childhood levodopa responsive basal ganglia disease may, in fact, comprise several different diseases.

The precise interrelations between response to levodopa, diurnal fluctuation, body movements during sleep, and catecholamine concentrations in cerebrospinal fluid remain to be clarified. Segawa *et al* performed polysomnography in four patients and found body movements mainly during stage 2 sleep.[2] A decrease in body movements during sleep was reported in Parkinson's disease and an increase in such movements occurs in Huntington's chorea and Gilles de la Tourette syndrome.[13] Increased body movements were found in our patients. These movements, however, occurred during REM rather than stage 2 sleep, and they seemed unresponsive to levodopa.

A unique finding was the presence of periodic leg movements during sleep in first degree relatives of three patients; we can find no other reports of familial periodic leg movements in an isolated form. A few instances of such movements have been seen in the familial restless leg syndrome.[14 15]

In summary, what characterises virtually all these reported cases is the onset between 1 year of age and puberty of a progressive and chronic motor handicap, which, in some cases, mimics spastic diplegia and in others mimics torsion dystonia. In most cases closer examination shows pronounced diurnal fluctuation of signs and symptoms, together with evidence of dystonic posturing; these are often associated with other signs of dysfunction of the basal ganglia such as choreiform movements, bradykinesia and mask like facies. Emotional disturbance, leading to referral for psychotherapy, may be common but does not contradict the diagnosis.

In cases with diurnal fluctuation a four day trial of levodopa in a daily dose of 10 to 20 mg/kg is mandatory, and an immediate improvement will usually confirm the diagnosis. In cases or families without diurnal fluctuation the diagnosis is more difficult. Either the polysomnographic findings of body movements during REM sleep, or the finding of abnormally low concentrations of dopamine or homovanillic acid, or both, in the cerebrospinal fluid, may predict response to levodopa. In case of doubt a four day trial should provide the answer.

We do not know what proportion of the cases presently diagnosed as late onset spastic paraplegia in chronic rehabilitation centres are, in fact, treatable cases of hereditary progressive dystonia. We believe that this possibility should not be ignored in view of the fact that three of our four patients and at least three other published cases had been referred to such care.

The presence of body movements during sleep in the patients and of periodic leg movements in healthy first degree relatives suggests that these two phenomena may be related although different expressions of a fundamental disorder of the basal ganglia. Such movement could serve as a genetic marker in affected families.

Dr Amos Korczyn of the Tel Aviv Municipal Hospitals was the first to suggest the correct diagnosis in case 1

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# Glycosylated haemoglobin and glucose intolerance in cystic fibrosis

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SUMMARY Sixty four patients, age range 1–20 years, with cystic fibrosis had their tolerance to glucose assessed according to their glycosylated haemoglobin ($HbA_1$) concentrations. Raised concentrations were found in 24 (37·5%). Oral glucose tolerance tests were performed on 21 patients with raised $HbA_1$ and 13 patients with normal $HbA_1$ concentrations. C peptide responses were also measured to assess islet cell function. Patients with normal $HbA_1$ had normal glucose tolerance and C peptide response. Seven of 21 patients with raised $HbA_1$ concentrations were glucose intolerant. The remaining 14 patients with raised $HbA_1$ concentrations had normal glucose tolerance but a reduced C peptide response, suggesting impaired islet cell function. There were no appreciable differences in the incidence of chest infections, respiratory function, and chest $x$-ray scores among patients with normal $HbA_1$ concentrations, raised $HbA_1$ concentrations, and normal oral glucose tolerant tests, and patients who were glucose intolerant. No correlation was found between $HbA_1$ concentration and age or Shwachman score. Measuring $HbA_1$ concentrations periodically is useful in detecting and monitoring glucose intolerance in patients with cystic fibrosis.

The reported incidence of glucose intolerance in patients with cystic fibrosis ranges from 8–75%. Insulin dependent diabetes occurs in 1–2%, 10 times the incidence in the normal population.[1] Glucose intolerance is thought to result from disruption of islet cells due to pancreatic fibrosis which progresses with increasing age and severity of the disease; consequently it is usually found only in older fibrocystic patients. Glucose intolerance may cause weight loss and may result in an increase in the incidence and severity of respiratory infections Impaired neutrophil function has been described in the presence of high blood glucose concentrations, and a correlation has been shown between prevalence of infection among diabetics and the degree of glucose control.[2–5] We could find no such reports concerning patients with cystic fibrosis.

Poor glucose control results in glycosylation of haemoglobin with a corresponding increase in plasma concentrations. In insulin dependent diabetes concentrations of $HbA_{1c}$ correlate well with glucose control over the preceding 1–2 months.[6] Caiger *et al* recently suggested that determining $HbA_1$ concentrations periodically may be useful in monitoring glucose intolerance in fibrocystic subjects.[7] Raised $HbA_1$ concentrations occur in such patients even when oral glucose tolerance tests give normal results.[8]

Islet cell function in fibrocystic patients has been investigated, usually by measuring insulin concentrations following a stimulation test.[9–12] C peptide is produced in equimolar proportions to insulin by cleavage of the pro insulin molecule in the $\beta$ cell of the pancreas; it has no primary biological activity Its main role seems to be to maintain the configuration of the insulin molecule. Unlike insulin, C peptide is not degraded by the liver and measurement of its activity gives a reasonable assessment of islet cell function [13] The half life is 11–35 minutes compared with that of insulin (4 3–9·8 minutes) For these reasons there is less variation in peripheral C peptide activity during oral glucose tolerance tests.

In this study we assessed the importance of raised concentrations of $HbA_1$ in patients with cystic fibrosis by performing oral glucose tolerance tests and investigating islet cell function by measuring the

C peptide response to the glucose challenge. We also examined the possible effects of glucose intolerance on cystic fibrosis.

## Patients and methods

Sixty four patients, with an age range of 1–20 years, who attended the cystic fibrosis clinic at Alder Hey Children's Hospital from January to June 1985 were entered into the study. The ethical committee approved the study, and consent was obtained.

HbA$_1$ and random blood glucose concentrations were estimated in all patients on entry into the study and repeated every two to six months. Patients with raised HbA$_1$ concentrations, and where possible, age matched patients in whom HbA$_1$ concentrations were normal, were admitted to the ward after an overnight fast for a standard oral glucose tolerance test. None of the patients was taking drugs that could influence glucose tolerance—for example, steroids or salbutamol—and none had acute infections at the time of the study. All had had an adequate intake of carbohydrate for at least three days before the glucose challenge. Glucose (1·75 g/kg, maximum 75 g) was given orally with 100–300 ml water. Blood was withdrawn through an intravenous cannula (which was maintained by an infusion of 0·9% saline) at 30 minute intervals from time 0 to 150 minutes for estimation of glucose concentrations and C peptide activity. Patients who were reluctant to be admitted for the oral glucose tolerance test were studied in the morning outpatient clinic. Blood from these patients was taken for estimation of glucose concentration at 0 and 120 minutes. The criteria used for the classification of the results of the glucose tolerance test depended on the fasting blood glucose concentration taken at these times.[14]

Glucose and HbA$_1$ concentrations were estimated in blood preserved with fluoride oxalate. Samples were stored at minus 10°C for up to one week before analysis. Glucose was measured using a glucose oxidase method (Yellow Springs Instrument) HbA$_1$ concentrations were determined by ion exchange column chromatography and spectrophotometry (Biorad haemoglobin A$_1$ by column test) and expressed as a percentage of the total haemoglobin The interassay standard deviation for this method was 0·68 and the coefficient of variation 5·7% The reference range for our laboratory is 5·3–8·8% for HbA$_1$, representing two SD limits of the mean in normal paediatric patients. A value of HbA$_1$ above 9% was regarded as raised. The C peptide activity was measured by radioimmunoassay at St Lukes Hospital, Guildford.[15] Heparinised blood was taken on ice and the serum separated and stored at −20°C before analysis. Assay sensitivity has been calculated at 0·037 nmol/l with interassay variation of 0·02–0·1 nmol/l.

The severity of each patient's disease was assessed using the Shwachman score,[16] pulmonary function tests, and chest $x$-ray score. Pulmonary function tests were performed regularly on all patients attending the clinic and included measurement of peak flow, forced vital capacity (FVC), and forced expiratory volume in one second (FEV$_1$). The chest $x$-rays were scored according to the Chrispin Norman scoring system.[17]

The incidence of severe chest infections over the past two years and the incidence of colonisation of the respiratory tract by *Pseudomonas* spp was determined from retrospective study of the case notes. A serious chest infection was defined as an episode resulting in an increase in cough or purulent sputum, or both, acute changes on the chest $x$-ray, and deterioration in pulmonary function necessitating admission to hospital.

Student's $t$ test was used to analyse the significance of differences between numbers, and the Mann-Whitney U test and Fisher's exact test for the differences between proportions.

## Results

A raised HbA$_1$ concentration (mean 10·6%, range 9·1%–17·5%) was found on entry into the study in 21 of the 64 patients attending the clinic, which indicated impairment of glucose control in 32·8% The mean (SD) HbA$_1$ concentration of the remaining 43 patients was 7·8 (0·9)%, range 5·9–8·8. These results are comparable with those obtained from 21 normal children admitted to Alder Hey Children's Hospital for routine operations (mean (SD) HbA$_1$ 7·4 (0·94)%, range 4·6–8·8). During the year after entry to the study, three more patients were found to have raised concentrations of HbA$_1$.

Oral glucose tolerance tests were performed in 34 patients, each of whom had between two to six measurements of HbA$_1$ in the year after entry to the study. These 34 patients included 21 of the 24 patients who had one or more raised HbA$_1$ measurements, in addition to 13 other patients with cystic fibrosis of similar age who had normal concentrations of HbA$_1$ The mean (SD) age of the two groups was 9·2 (5·8) years and 10·5 (5·1) years, respectively. Seven of the 21 patients (33·3%) with raised HbA$_1$ concentrations had abnormal glucose tolerance test results; three produced a diabetic response and two of these were insulin dependent (Fig 1). All 13 patients with normal HbA$_1$ concentrations had normal oral glucose tolerance test

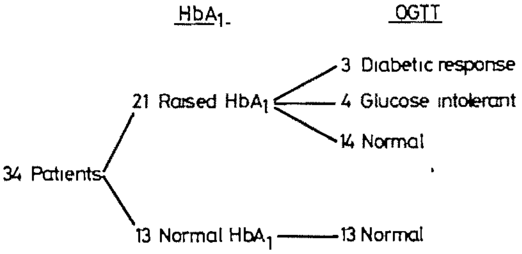

Fig 1 *Results of glycosylated haemoglobin and oral glucose tolerance tests in 34 patients with cystic fibrosis*

results. These differences are significant (Fisher's exact test, $p<0·05$).

To investigate the importance of a raised $HbA_1$ concentration and to examine islet cell function and the effects of glucose intolerance in more detail all the patients with cystic fibrosis were divided into three groups according to the result of the glucose tolerance test and the highest $HbA_1$ concentration recorded during the previous year: group 1 normal subjects had $HbA_1$ concentrations within the normal range and a normal oral glucose tolerance test; group 2 had a raised serum $HbA_1$ concentration and a normal oral glucose tolerance test result; and group 3 had a raised concentration of $HbA_1$ and an abnormal oral glucose tolerance test result.

The mean (SD) age of patients in group 1 (n=13) was 10·5 (5) years (range 3–19·8), in group 2 (n=14) 7 (4·7) years (range 2·3–15·8), and in group 3 (n=7) 13·6 (5·7) years (range 3·8–19·5). The Table shows the mean fasting concentrations of glucose values at the time of the oral glucose tolerance test; the differences between these groups were not significant There was, however, a significant difference between the mean $HbA_1$ concentrations at the time of the oral glucose tolerance test in both group 2 ($p<0·05$) and group 3 ($p<0·01$) when compared with the normal group (Table). Blood for estimation of $HbA_1$ concentration was taken at time zero.

Table *Mean (SD) fasting blood glucose concentrations and % glycosylated haemoglobin in 34 patients with cystic fibrosis*

| | *Fasting blood glucose concentration (mmol/l)* | *% Glycosylated haemoglobin* |
|---|---|---|
| Normal subjects (n=13) | 4·2 (0·4) | 7·2 (0·8) |
| Patients with raised concentration of glycosylated haemoglobin (n=14) | 3·9 (0·5) | 8·8 (1·3) |
| Patients with glucose intolerance (n=7) | 4·5 (0·9) | 9·1 (2·2) |

Detailed analysis of the response of the islet cells to the glucose tolerance test was only possible in 24 of the 34 patients. The 10 patients not included completed the test in the clinic, having blood taken at time 0 and 120 minutes only Figure 2 shows the number of patients in each group completing the full test This graph shows the mean (SE) glucose concentration at each sampling time for each group during the oral glucose tolerance test. Patients in groups 1 and 2 produced similar glucose profiles, but the mean peak glucose concentration was reached at 30 minutes in group 1 and at 60 minutes in group 2. There were similar glucose concentrations at 120 minutes (5·6 mmol/l and 5·3 mmol/l, respectively). The peak mean glucose concentration of patients in group 3 was reached at 90 minutes with a mean glucose concentration of 11·7 mmol/l at 120 minutes.

Figure 3 shows the mean C peptide activity at each sampling time for each of the groups of

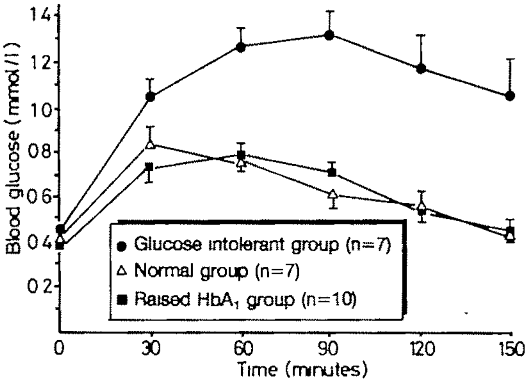

Fig. 2 *Mean (SEM) glucose concentrations during oral glucose tolerance tests in 24 patients with cystic fibrosis*

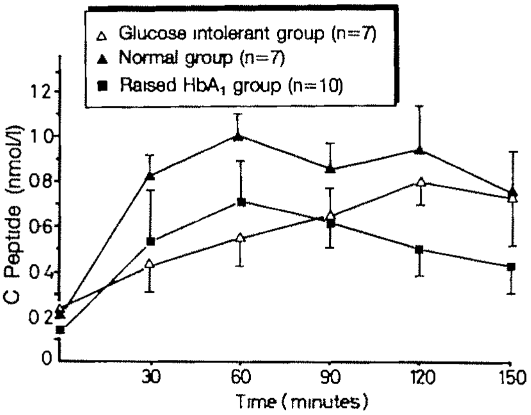

Fig 3 *Mean (SEM) C peptide concentrations during oral glucose tolerance tests in 24 patients with cystic fibrosis*

patients. There was a rapid increase in C peptide activity in patients in the normal group to a peak at 60 minutes followed by a gradual fall. A slow rise, also with a peak at 60 minutes, was seen in group 2, but lower concentrations were present at all times. The rise in C peptide activity in group 3 was delayed, with a peak at 120 minutes; only two of the seven patients produced peak concentrations before 120 minutes (at 60 and 90 minutes). In the first two groups 11 of 17 had peak values at or before 60 minutes. Significant differences ($p<0·05$) were seen between measurements of C peptide activity at 30 and 60 minutes between groups 1 and 3 in addition to that between groups 1 and 2 at 120 minutes ($p<0·05$)

Two girls, aged 17 and 19 required insulin for symptomatic glucose intolerance; this was started two and four years before the study. Doses of insulin of 0·8 and 1·3 units kg/24 hours, respectively, were needed to achieve adequate control. On the day of the oral glucose tolerance test the morning dose of insulin was omitted following the overnight fast Fasting glucose concentrations of 5·0 and 3·0 mmol/l were obtained. Maximum recorded C peptide activity occurred at 120 minutes in both, with values of 1·1 nmol/ and 0·3 nmol/l respectively. Neither had episodes of hyperglycaemic ketoacidosis.

The peak $HbA_1$ concentration for each of the 34 patients recorded during the year of the study correlated significantly with the $HbA_1$ concentration measured in blood taken at the time of the oral glucose tolerance test ($r=0·47$ $p<0·05$). There was a negative correlation between $HbA_1$ concentrations and total C peptide activity, but this did not reach significance.

Patients with glucose intolerance were not significantly different from the normal group in respect of Shwachman score, number of serious chest infections, colonisation with *Pseudomonas* spp, lung function, and chest *x*-ray scores. The body mass index and height for age of patients among the groups did not differ significantly

## Discussion

When patients with cystic fibrosis attending Alder Hey Children's Hospital were screened for evidence of glucose intolerance, 24 of 64 (37·5%) were found to have raised $HbA_1$ concentrations Glucose intolerance indicated by a standard oral glucose tolerance test was found in 33% of the patients assessed who had one or more raised measurements of $HbA_1$ concentration. All the patients who had consistently normal $HbA_1$ concentrations also had normal glucose tolerance. Dividing the patients into three groups enabled more detailed comparison to be made of the islet cell function as assessed by the blood glucose concentrations and C peptide activity during the oral glucose tolerance test.

The glucose profiles obtained from concentrations in blood measured during the oral glucose tolerance test groups 1 and 2 were similar, with comparable glucose concentrations recorded at 120 minutes Differences were found in the islet cell response to the oral glucose load, however, when measurements of the C peptide activity were compared. Group 2 produced a slower rise in C peptide activity following the glucose load, with lower C peptide activity recorded at all times This indicated impaired β cell reserve in patients with raised $HbA_1$ concentrations alone

Peak glucose concentrations were reached at 30 minutes in group 1 and at 60 minutes in group 2, with peak C peptide activity in both groups at 60 minutes. In a normal population peak glucose concentrations occur at 30 minutes[9 18 19] and peak C peptide activity between 30 and 60 minutes[18–20] after an oral glucose load

The mean (SD) rise in C peptide activity was 1·01 (0·2) nmol/l in the group of patients who had normal $HbA_1$ concentrations and normal glucose tolerance This compares with the range of mean values (0·9–2 2 nmol/l) recorded in normal adults.[18–20] Low immunoreactive insulin responses to glucose loads have been reported in patients with cystic fibrosis[9 10] By simultaneously measuring C peptide activity and insulin concentrations, Mohan *et al* showed that lower insulin concentrations in patients with cystic fibrosis are likely to be due to pancreatic β cell hypofunction rather than increased degradation of insulin in the liver.[21] Increased responsiveness to insulin in peripheral tissue has been suggested as a cause in patients with cystic fibrosis,[10] with an increase in the number and affinity of insulin receptors[22] The data, are however, conflicting.[11]

The glucose intolerant patients showed peak C peptide activity at 120 minutes, indicating defective release of insulin. These results agree with those obtained by Handwerger *et al*[9] The two insulin dependent patients studied both produced peak C peptide activity at 120 minutes. The patient who had been insulin dependent for two years, requiring insulin 0·8 units/kg/24 hours, produced a peak C peptide activity of 1·1 nmol/l. The other, an older patient who had been insulin dependent for four years and needed 1·3 units/kg/24 hours, produced a delayed poor response with peak activity of only 0·3 nmol/l, possibly indicating progressive deterioration in β cell function. Neither had episodes of ketoacidosis, and there was no family history of diabetes in either patient. Although the insulin requirements in patients with cystic fibrosis who develop diabetes are high (0·6–3·3 units/kg/day),[1] episodes of ketoacidosis do not occur. This has been explained by a reduced dietary fat intake in these patients, and the inability of the pancreas to produce sufficient glucagon. Glucagon directly opposes the action of insulin producing glycogenolysis, gluconeogenesis, and lipolysis. In diabetic patients with relatively severe diabetic ketoacidosis absolute hyperglucagonaemia has been reported[23] Impaired glucagon production has been shown in patients with cystic fibrosis.[11]

We found a significant correlation between fasting and peak C peptide activity. This has also been shown in diabetic patients[24] and indicates that the production of C peptide follows the law of the initial value, which states that the magnitude of the response is related to the concentration before stimulation.[25] Fasting C peptide activity recorded in the three groups did not, however, differ significantly. There were also no significant differences in the increase and peak of C peptide activity achieved.

The highest recorded $HbA_1$ concentration for each patient obtained during the study year correlated significantly with the $HbA_1$ concentration measured at time zero during the oral glucose tolerance test, indicating a persistent increase in $HbA_1$ concentrations. A negative correlation was found between the $HbA_1$ concentration recorded at the time of the oral glucose tolerance test and the sum of C peptide activity Although this did not reach significance, Bistritzer *et al*[12] found a significant negative correlation between the sum of the insulin concentrations during the oral glucose tolerance test and the $HbA_1$ concentration in 11 patients with cystic fibrosis. This suggests that the lower the insulin response to a glucose challenge, the higher the $HbA_1$ concentration.

The commercial method (Biorad) used in this study estimates total glycosylated haemoglobin. No attempt was made to remove the labile fraction, which has been shown to correlate with the glucose concentration at the time of sampling.[26] To reduce this complicating factor blood for $HbA_1$ assay was taken at time zero during the oral glucose tolerance test. No significant differences in the fasting glucose concentrations were found between the groups We have shown that $HbA_1$ concentration is useful in assessing glucose tolerance in patients with cystic fibrosis High concentrations of $HbA_1$ indicate impaired β cell reserve with decreased or delayed insulin release

There was no correlation between raised $HbA_1$ and age, as found by Bistritzer *et al.*[12] For this reason all patients with cystic fibrosis should be assessed periodically for glucose intolerance. High concentrations of fetal haemoglobin in newborns and in some 1–2 year olds may produce falsely raised $HbA_1$ concentrations because fetal haemoglobin elutes with $HbA_1$ as a fast band on ion exchange column chromatography. Alternative methods of measuring $HbA_1$ that eliminate this error should be used in patients below the age of 2 years. The youngest glucose intolerant patient in our study was 3 years 8 months old. He had a $HbA_1$ concentration of 10·3% and blood glucose at 120 minutes of 9·3 mmol/l. He did not have glycosuria and was asymptomatic. His progress is being followed closely.

The clinical course of insulin dependent diabetes mellitus in cystic fibrosis is mild. Ketoacidosis does not occur and complications are rare. Provided growth is adequate and the patient is not troubled by symptomatic hyperglycaemia, the motivation to achieve good control is poor. The effect of glucose intolerance on infection in patients with cystic fibrosis has not been investigated.

Rayfield *et al* found a striking correlation between the overall prevalence of infection and mean plasma glucose concentrations in insulin dependent diabetes.[5] In vitro studies have shown impairment of opsonisation,[4] neutrophil adherence,[2] chemotaxis,[3] phagocytosis,[4] and bactericidal activity[5] in the presence of hyperglycaemia. Glucose intolerance may lead to an increase in the prevalence and severity of respiratory infections in patients with cystic fibrosis. In this study, however, no significant differences were found in the number of chest infections, the prevalence of colonisation with *Pseudonomas* spp, respiratory function, or the Shwachman score in the patients with cystic fibrosis and glucose intolerance compared with those with normal glucose intolerance.

In conclusion, periodic assessment of $HbA_1$ concentration is useful in determining the presence of glucose intolerance in patients with cystic fibrosis and in monitoring its course Evidence of impaired β cell reserve was found in patients with raised $HbA_1$ concentrations, 33% of whom were glucose intolerant during an oral glucose tolerance test. Impaired neutrophil function as a result of hyperglycaemia may lead to an increase in the number and severity of chest infections. We did not, however, show such an effect in this study, and further in vitro and in vivo studies are necessary to investigate this.

We thank Mrs D Bolger for preparing this paper

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# Familial Hashimoto's thyroiditis with kidney impairment

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SUMMARY A 12 year old boy and his two sisters with Hashimoto's thyroiditis and renal impairment were studied. Three generations of this family had autoimmune thyroid disease: Graves' disease was diagnosed in the first generation, and the second and third generations had thyroid enlargement with abnormal thyroid function and immunological abnormalities. The disease in this family could not be explained simply by the types of human leucocyte antigens found. Renal disease in autoimmune thyroid disease is uncommon, treatment difficult, and the prognosis unknown.

The proteinuria disappeared in all three children during the three and a half years of follow up, which implies that the renal impairment may be transitory in some patients.

There are five autoimmune thyroid diseases: Hashimoto's thyroiditis, primary myxoedema, non-toxic goitre with detectable thyroid growth stimulating immunoglobulins, Graves' disease, and ophthalmic Graves' disease.[1–5] These diseases commonly run in families, and relatives of patients with autoimmune thyroid disease often have an increased prevalence of antithyroid antibodies.[6 7] These patients may also have circulating immune complexes with thyroglobulin and antithyroglobulin [8 9] In a few patients kidney damage and nephrotic syndromes have been reported.

We describe a family in which autoimmune thyroid diseases were found in three generations, with a variety of autoimmune abnormalities and evidence of immune complex nephritis The course of the kidney diseases in these patients may imply that kidney impairment in autoimmune thyroid diseases is transitory, though a longer period of follow up is needed to confirm this.

## Details of family

The propositus was referred to the outpatient clinic of the Department of Paediatrics B at the age of 11 years 9 months because of neck swelling for the past two months. The only abnormality found on physical examination was a large goitre (Table 1). Height and weight were on the 75th centile, and pubertal stage was Tanner's stage II.[10] Pertinent laboratory

Table 1 *Evaluation of thyroid function and results of urine analysis at first examination*

| | *Goitre grading*[20] | *Free thyroxine (pmol/l)* | *Total triiodothyronine (nmol/l)* | *Thyrotrophic hormone (mU/l)* | |
|---|---|---|---|---|---|
| | | | | *Basal* | *Peak (after intravenous bolus of 100 μg/m² thyrotropin releasing hormone)* |
| Father (II-3) | Easily palpable | 23 2 | 2 16 | 4 2 | 14 0 |
| Mother (II-4) | Easily palpable | 18 0 | 1 69 | 2 8 | 19 0 |
| Siblings | | | | | |
| III-1 | Grade 4 | 61 8 | 6 78 | 5 2 | 6 1 |
| III-2 (propositus) | Grade 4 | 15 4 | 1 54 | 23 8 | 100 0 |
| III-3 | Grade 3 | 23 2 | 3 08 | 11 6 | 23 0 |
| III 4 | Grade 2 5 | 21 9 | 2 62 | 6 5 | 16 1 |

Normal values free thyroxine 8–29 pmol/l, total tri-iodothyronine 1 54–3 08 nmol/l, thyroid stimulating hormone <6 mU/l data are summarised in Table 1 and are compatible with the diagnosis of latent hypothyroidism. Histological examination of a needle biopsy specimen of the gland confirmed the diagnosis of Hashimoto's thyroiditis, and treatment with thyroxine sodium 100 µg daily was started.

Six months after his first visit he had puffy eyes and pitting oedema of the legs and had gained a lot of weight. Haematological investigations showed an erythrocyte sedimentation rate of 106 mm in the first hour, a white cell count of 7·6×10⁹/l, a haemoglobin concentration of 1·55 mmol/l, and a platelet count of 440×10⁹/l (the differential was normal). Biochemical investigations showed a urea nitrogen concentration of 4·6 mmol/l, creatinine concentration of 39·8 µmol/l, potassium concentration of 4·3 mmol/l, sodium concentration of 142 mmol/l, chlorine concentration of 107 mmol/l, calcium concentration of 1·9 mmol/l, and phosphorus concentration of 1·68 mmol/l. Total protein concentration was 53 g/l, that of albumin being 23 g/l. Cholesterol concentration was 9·06 mmol/l, with total lipids of 7·5 g/l and triglycerides of 2·75 mmol/l. Repeated analysis of his urine showed obvious proteinuria (>230 mg/hour/m$^2$) but no haematuria. Because these findings suggested a nephrotic syndrome renal biopsy was performed. On histological examination there was irregular thickening of the glomerular capillary walls with epimembranous hyaline depositis and endocapillary hypercellularity, which suggested a mixed membranous and proliferative glomerulonephritis. Studies of the renal biopsy specimen with immunofluoresence and immunoperoxidase staining showed glomerular capillary clumps of thyroglobulin, IgG, IgM, C3, and kappa and lambda chains of comparable distribution.

Treatment was begun with cyclophosphamide 125 mg daily for eight weeks and prednisone 60 mg daily for four weeks, the prednisone to be reduced gradually to 40 mg every other day. At that time thyroxine sodium was stopped. The child was followed up for one year after this regimen was started. During this period the goitre, which had become smaller during the treatment with thyroxine sodium, enlarged; the concentration of thyroid stimulating hormone, which had dropped to 3·6 mU/l, rose to the pretreatment value of 60 mU/l. Treatment with thyroxine sodium was therefore started again. After this treatment started the concentration of protein in his urine slowly but progressively reduced, and 18 months later it had dropped to 85 mg/hour/m$^2$; after six further months it was down to 32 mg/hour/m$^2$. After two and a half years of treatment the proteinuria had disappeared. During this period concentrations of antithyroid antibodies, both antimicrosomal and antithyroglobulin, decreased to a constant titre of 1/80 to 1/160. At 15½ years old the child had a small goitre, but otherwise physical examination showed no abnormality and his growth and pubertal stage were appropriate for his age.

Three generations of the family were examined (Figure); all were of Ashkenazi-European origin. Seven subjects (I-1, 3, 4, and II-1, 2, 5, 6) were apparently healthy with no clinical evidence of thyroid dysfunction; no laboratory investigations were performed in these subjects. Other siblings of subject I-4 had died in the holocaust. The child's paternal grandmother (I-2) had had Graves' disease for the past 10 years, she was being treated with methimazole and was euthyroid when examined. One of the maternal grandmother's sisters (I-5) also had Graves' disease. She had undergone subtotal thyroidectomy 20 years previously and was not taking any antithyroid drugs. The parents of the propositus (II-3, 4) both 36 years old and unrelated, were thought to be in good health; on examination, however, their thyroid glands were mildly enlarged. No other findings suggestive of altered thyroid function were found. Pertinent data on them are summarised in Tables 1, 2, and 3. Results of haematological investigations and urine analysis and blood glucose concentrations were normal in the parents.

The propositus had three sisters (III-1, 3, 4), who were aged 12 years 9 months, 9 years 3 months, and 6 years when first examined. They all had similar 'neck swellings', which had appeared at about the same time as that of the propositus. Their medical history was unremarkable. Table 1 shows their goitre grading.[11] The eldest sister (III-1) had a mild

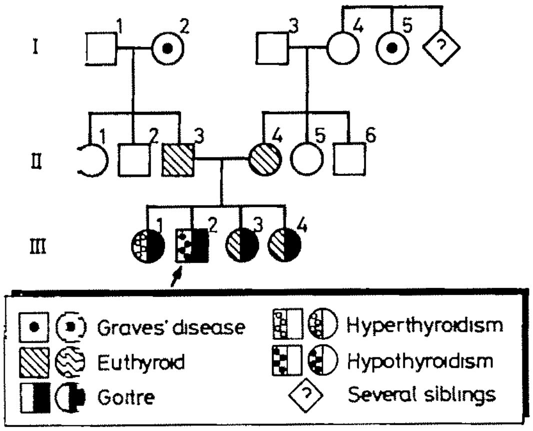

Figure *Pedigree of family with autoimmune thyroid disease and kidney impairment*

Table 2 *Immunological investigations at first evaluation (1983) and 18 months later (1984)*

| | *Thyroid* | | | | *Stomach antiparietal cells* | | *Antinuclear antibodies* | | *Circulating immune complexes (PEG method)* | | *Proteinuria (mg/hour/m$^2$)* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Antithyroglobulin* | | *Antimicrosomal* | | *1983* | *1984* | *1983* | *1984* | | | *1983* | *1984* |
| | *1983* | *1984* | *1983* | *1984* | | | | | *1983* | *1984* | | |
| Father | – | – | 400 | 400 | + | + | – | – | 116 | 59 | Neg | Neg |
| Mother | 80 | 80 | 400 | 400 | + | + | 20 | 10 | 65 | 45 | Neg | Neg |
| Siblings | | | | | | | | | | | | |
| III-1 | 640 | 1280 | 400 | 1600 | – | – | – | 40 | 124 | 49 | 13 4 | 9 4 |
| III 2 (propositus) | 1280 | 10000 | 1600 | 1600 | – | – | – | – | 72 | 41 | 230 | 85 |
| III-3 | 40 | 160 | 100 | 100 | – | – | – | – | 215 | 85 | 10 8 | Neg |
| III-4 | – | 160 | – | 1600 | – | – | – | – | 104 | 59 | Neg | Neg |

Normal values for circulating immune complexes 100 μg IgG equivalent ml
Reciprocal titres obtained by haemagglutination with Wellcome Thymune kits

Table 3 *Human leucocyte antigen haplotypes*

| | *HLA-A* | *HLA-B* | *HLA-DR* |
|---|---|---|---|
| Grandmother (I-2) | 28/29 | 14/7 | 6/2 |
| Aunt (I-5) | 26/26 | 35/17 | 4/5 |
| Father (II-3) | 2/29 | 14/7 | 7/2 |
| Mother (II-4) | 24/28 | 14/14 | 5/1 |
| Siblings | | | |
| III-1 | 2/28 | 14/14 | 7/1 |
| III-2 (propositus) | 2/24 | 14/14 | 7/5 |
| III/3 | 2/24 | 14/14 | 7/5 |
| III-4 | 29/28 | 7/14 | 2/1 |

tremor. The results of investigations suggested that she had hyperthyroidism, and she was given prophylthiouracil 200 mg a day, which was gradually reduced as function of the hypophyseal axis improved (shown by repeated estimation of thyrotrophin releasing hormone concentrations). Proteinuria of 9·4–13·4 mg/hour/m$^2$ was found, but there was no other clinical or laboratory evidence of nephrotic syndrome The proteinuria remained within this range after the antithyroid drugs had been stopped, but one and a half years later no protein could be found in the urine. Physical examination of the two other sisters showed no obvious abnormality. One (III-3) had a slightly increased basal concentration of thyroid stimulating hormone which later returned to normal. Repeated urine analysis showed a proteinuria of 10·8/hour/m$^2$, but this disappeared spontaneously within several months. The initial laboratory investigations of the other sister (III-4) all yielded normal results. Table 2 summarises the immunological data on the family, and the human leucocyte antigen haptotypes are shown in Table 3. Renal biopsies were not performed for two of the sisters (III-1 or III-3).

## Discussion

In this family evidence of autoimmune thyroid disease was found in three generations. Graves' disease was diagnosed (in another hospital) in two patients of the first generation; in the second generation slightly enlarged thyroid glands were found in two patients, as well as mildly raised titres of autoantibodies against thyroid, stomach, and nuclei. In the third generation the children had goitres and autoantibodies as well as increased concentrations of circulating immune complexes, but the clinical manifestations differed and included hyperthyroidism, latent hyperthyroidism, and euthyroidism.

The occurrence of Graves' disease and Hashimoto's thyroiditis in the same family and the increased prevalence of autoantibodies in relatives of patients with Hashimoto's thyroiditis are well documented,[6 7] as are the occurrence of Hashimoto's thyroiditis in a parent and offspring, in twins, and in triplets.[12] Such an extensive distribution of autoimmune thyroid diseases in one sibship, however, with such variability in the clinical and immunological presentations, is unusual. Both parents had evidence of autoimmune thyroid disease; the mother's haplotype included $DR_5$, which is associated with Hashimoto's thyroiditis.[13 14] The presence of this antigen, however, can explain the symptoms of only two of the children (III-2 and 3) and not of the other two (III-1 and 4). None of the haplotypes of either of the women with Graves' disease (I-2 and I-5) was transmitted to generation III. HLA B14, which is frequently found in Israelis, was present in all the affected family members except one (I-5). B14 has not, however, been reported previously in association with Hashimoto's thyroiditis. It is possible that on both sides of this family there was a predisposition to the immunological defect that is responsible for Hashimoto's thyroiditis, and that this was transmitted vertically to the third generation. Because of the synchronous appearance of the goitre in the siblings it may also be that a common event such as a viral infection triggered the autoimmune mechanism in the children, and possibly in the parents as well.

The association of immune complex nephritis with Hashimoto's thyroiditis as in the propositus is rare.[9,13–18] Membranoproliferative glomerulonephritis with the deposition of immune complexes with thyroglobulin as the antigen was reported in these patients. In one case thyroglobulin was also shown in the circulating immune complexes, with a positive correlation between the serum concentrations of these complexes and the severity of the disease.[9] It was suggested that the glomerular disease was caused by trapping of nephritogenic immune complexes from the blood stream. In our propositus thyroglobulin was found in the glomerular capillary clumps but not in the circulating immune complexes. Glomerular deposits are formed in situ by the reaction of free antibody with a fixed antigenic constituent of the glomerular capillary wall.[19] Proteinuria alone, without the nephrotic syndrome, has been reported in two of 27 patients with Hashimoto's thyroiditis,[20] but the natural course of this type of kidney disease is unknown. Some patients with kidney disease underwent total thyroidectomy with the aim of eliminating the antigen. In these cases the proteinuria was not eliminated during a follow up course of several months[13,16] but the circulating antimicrosomal and antithyroglobulin antibodies disappeared[16] Our patients have now been followed up for three and a half years. None of these three children with renal impairment had proteinuria when last seen. Although this is after a short term follow up, it may indicate either that thyroidectomy should not be performed in all patients or that it should not be done in the early stages of the disease. Interestingly, in some patients with Graves' disease the immune complex glomerulonephritis was associated with the antithyroid treatment,[14,21] either radioiodine or drugs Whether such treatment has a role in the kidney disease or whether the association is coincidental is unknown.

Physicians must be aware of the possibility of impairment of the kidneys in autoimmune thyroid diseases and of the importance of doing repeated urine analyses. Only through better diagnostic accuracy can management and prognosis of these patients be improved.

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# Comparison of budesonide and beclomethasone dipropionate for treatment of asthma

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SUMMARY Beclomethasone dipropionate (BDP) and budesonide (BUD) were each given in a dose of 200 μg twice daily by metered dose inhaler to 10 asthmatic children already dependent on treatment with steroids. In a double blind randomised crossover study each course lasted one month. No clinically important differences were found between the two treatments when symptom scores, symptom free days, additional use of salbutamol, and results of lung function tests were considered. Metyrapone mildly reduced the plasma concentration of 11-deoxycortisol in two patients during treatment with budesonide, and in four during treatment with beclomethasone. It is concluded that although they are usually safe, both drugs may cause mild adrenal suppression when given in a dose of 200 μg twice daily.

Inhaled beclomethasone dipropionate (BDP) is effective treatment for asthma in children.[1-4] Recently a new non-halogenated corticosteroid aerosol, budesonide, has been shown to be effective in treating chronic asthma in adults[5] and in children.[6 7] Budesonide need only be given twice daily, compared with the four doses of beclomethasone that are usually required each day.

We therefore set up a trial to compare the efficacy of the two drugs when both were given twice daily to asthmatic children already dependent on treatment with steroids. In addition, we evaluated the influence of the two drugs on the function of the pituitary adrenal axis in view of reports that BDP could cause adrenal suppression.[8 9]

## Patients and methods

Ten asthmatic children aged between 9 and 15 and already dependent on treatment with steroids were included in the study. They were all within the normal ranges of height and weight for their ages. Nine patients had already been receiving BDP (400 μg daily) for two months to four years (mean 1·7 years), and one patient started treatment with inhaled corticosteroids at the beginning of this study. No patient had received oral steroids for more than a total of 20 days in the previous year, and none for the last month

The trial was a double blind randomised crossover study with one month each of treatment by BUD or BDP 200 μg twice daily using a conventional pressurised aerosol without a spacer. The treatment protocols were as follows (i) BDP 200 μg (four puffs) twice daily and placebo BUD four puffs twice daily (every 12 hours); and (ii) BUD 200 μg (four puffs) twice daily and placebo BDP four puffs twice daily. The order of the treatments was decided at random. In addition to BUD and BDP, the children were allowed free use of salbutamol given by pressurised aerosol. Each child used a standard diary card to record diurnal and nocturnal symptoms and drug use throughout the trial.[10] In addition, peak expiratory flow rates were measured each morning and evening before taking the drugs using the Wright Mini Peak Flow Meter At the end of each month measurements of forced expiration and whole body plethysmography were made in the laboratory

A 24 hour urine collection was made at the end of each month for measurement of the excretion of tetrahydrocortisone glucosiduronate (THE) and tetrahydrocortisol glucosiduronate (THF) by radioimmunoassay [11] Concentrations of cortisol, adrenocorticotrophic hormone (ACTH) and 11-deoxycortisol in plasma were measured at the end of each month of treatment before and 10 hours after a single oral dose of 30 mg/kg of metyrapone, using a sensitive radioimmunoassay described previously.[12-15]

Table 1 *Results after taking beclomethasone for one month*

| | *Case No* | | | | | | | | | | *Mean (SEM)* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* | *9* | *10* | |
| No of doses of salbutamol | 6 | 0 | 0 | 35 | 0 | 0 | 0 | 6 | 6 | 4 | 9 (4) |
| Days free of symptoms (% of total) | 0 | 100 | 79 | 0 | 93 | 100 | 100 | 0 | 86 | 71 | 63 (14) |
| Symptom score (% of maximum) | 16 | 0 | 4 | 24 | 1 | 0 | 0 | 20 | 1 | 7 | 8 (3) |
| Peak expiratory flow rate* | 79 | 112 | 122 | 87 | 108 | 74 | 117 | 68 | 111 | 109 | 101 (5) |
| Maximum expiratory flow rate at 50% vital capacity* | 19 | 45 | 58 | 62 | 51 | 46 | 63 | 61 | 59 | 74 | 58 (3) |
| Forced expiratory volume in 1 second* | 46 | 74 | 37 | 90 | 90 | 64 | 91 | 81 | 85 | 101 | 85 (3) |
| Specific airways conductance* | Not done | Not done | 150 | 69 | 41 | 50 | 50 | 100 | 53 | 41 | 69 (13) |

*Given as % of predicted value

Table 2 *Results after taking budesonide for one month*

| | *Case No* | | | | | | | | | | *Mean (SEM)* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* | *9* | *10* | |
| No of doses of salbutamol | 14 | 0 | 0 | 36 | 0 | 0 | 2 | 2 | 8 | 0 | 8 (5) |
| Days free of symptoms (% of total) | 0 | 100 | 100 | 36 | 86 | 100 | 100 | 14 | 71 | 86 | 69 (12) |
| Symptoms score (% of maximum) | 20 | 0 | 0 | 27 | 2 | 0 | 0 | 11 | 4 | 1 | 7 (3) |
| Peak expiratory flow rate* | 97 | 120 | 118 | 87 | 106 | 83 | 120 | 79 | 106 | 110 | 103 (4) |
| Maximum expiratory flow rate at 50% vital capacity* | 66 | 51 | 48 | 77 | 59 | 60 | 54 | 52 | 51 | 82 | 62 (3) |
| Forced expiratory volume in 1 second* | 92 | 77 | 90 | 105 | 99 | 92 | 76 | 84 | 84 | 101 | 90 (3) |
| Specific airways conductance* | Not done | Not done | 120 | 49 | 46 | 72 | 70 | 100 | 35 | 35 | 66 (11) |

*Given as % of predicted value

Table 3 *Excretion of tetrahydrocortisol glucosiduronate and tetrahydrocortisone glucosiduronate after taking beclomethasone and budesonide*

| | *Case No* | | | | | | | | | | *Mean (SEM)* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* | *9* | *10* | |
| Beclomethasone | | | | | | | | | | | |
| Tetrahydrocortisol glucosiduronate (mg/24 hours)* | 0 87 | 0 93 | 0 42 | 0 19 | 0 97 | 0 57 | 0 45 | 1 09 | 0 71 | 0 47 | 0 67 (0 10) |
| Tetrahydrocortisone glucosiduronate (mg/24 hours)† | 1 26 | 1 30 | 0 69 | 0 54 | 3 18 | 0 39 | 0 79 | 1 18 | 2 00 | 0 51 | 1 18 (0 27) |
| Urine volume (ml/24 hours) | 750 | 1300 | 723 | 1000 | 790 | 1470 | 790 | 810 | 1050 | 1350 | 1004 (88) |
| Budesonide | | | | | | | | | | | |
| Tetrahydrocortisol glucosiduronate (mg/24 hours)* | 1 58 | 0 43 | 0 45 | 0 40 | 0 88 | 0 33 | 0 17 | 0 38 | 1 19 | 0 39 | 0 62 (0 14) |
| Tetrahydrocortisone glucosiduronate (mg/24 hours)† | 1 44 | 0 73 | 0 33 | 0 63 | 3 11 | 0 39 | 0 31 | 1 54 | 3 03 | 0 33 | 1 17 (0 35) |
| Urine volume (ml/24 hours) | 750 | 720 | 950 | 1160 | 1020 | 1130 | 310 | 650 | 1350 | 690 | 873 (97) |

Mean (SD) normal values, mg/24 hours *1 34 (0 71), †1 25 (0 91)

Comparisons between numbers were made using the paired *t* test, differences being regarded as significant if the p value was $<0{\cdot}05$.

## Results

Thirteen children entered the trial, but three were withdrawn during the first two weeks because of acute exacerbations of asthma requiring treatment with oral steroids. One child was receiving BUD and the other two BDP. Tables 1 and 2 show that for the remaining 10 patients there were no significant differences between treatments when measurements of forced expiratory volume in one second, maximum expiratory flow at 50% vital capacity, and specific airways conductance at the end of each month were considered, neither were there any differences in diary symptom score, number of symptom free days, mean morning and evening peak expiratory flow rates, and need for additional salbutamol for the second two weeks of each month. Table 3 shows the mean rates of excretion of THE and THF inclusive; there were no significant differences between treatments and all the individual values were within the normal ranges with both drugs.

Figures 1 and 2 show the basal concentrations of cortisol, 11-deoxycortisol, and adrenocorticotrophic hormone (ACTH) in plasma before and after a single dose of metyrapone. Concentrations of cortisol and ACTH were within normal limits in both months when BDP and BUD were administered 11-deoxycortisol increased normally in response to metyrapone in six children receiving BDP and eight receiving BUD. ACTH concentrations increased in most of the patients, but there was no correlation with the concentration of 11-deoxycortisol The response of cortisol to metyrapone varied.

## Discussion

We have shown that BUD is as effective as BDP for

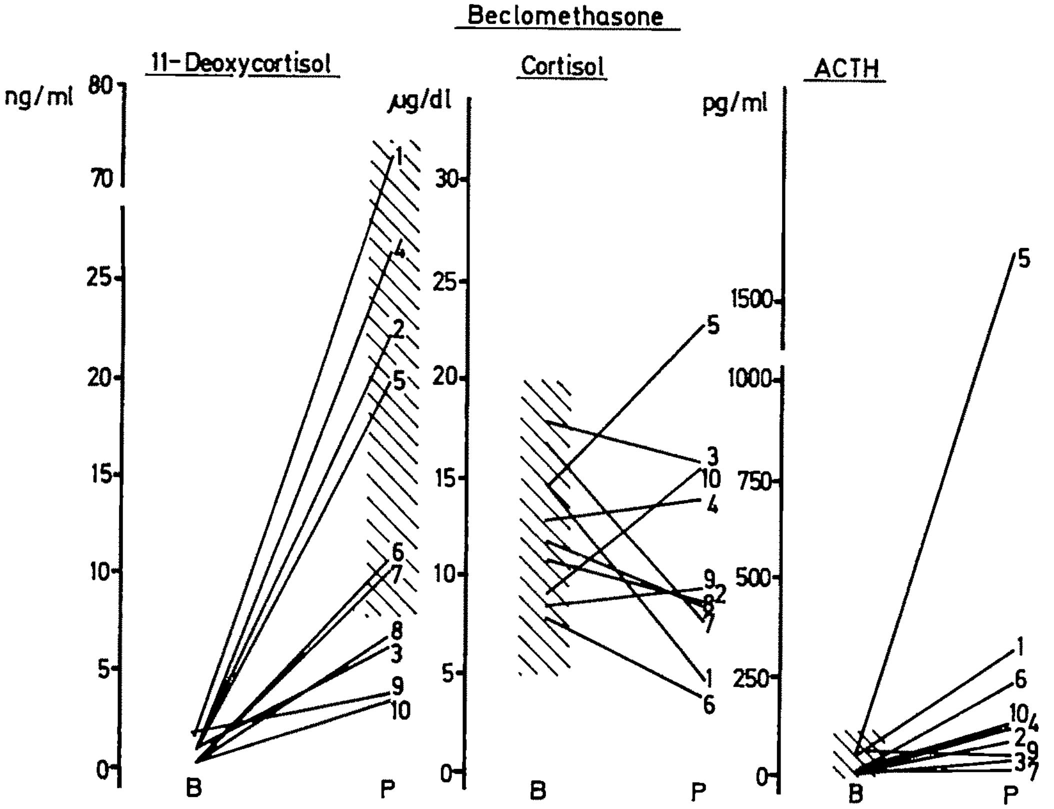

Fig 1 *Serum concentrations of 11-deoxycortisol, cortisol, and adrenocorticotrophic hormone before and after one dose of metyrapone during treatment with beclomethasone*
*B = basal, P = after metyrapone, shaded area = mean (SD) normal concentration*

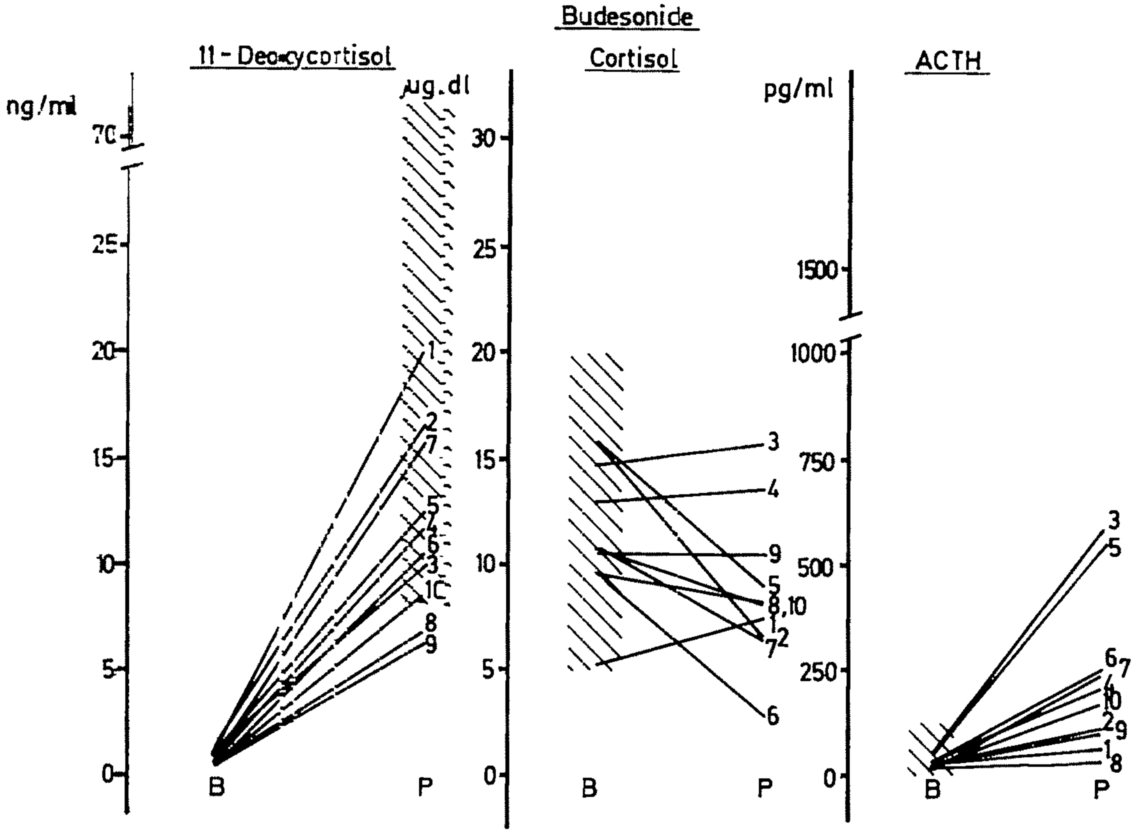

Fig 2 *Serum concentrations of 11-deoxycortisol, cortisol, and adrenocorticotrophic hormone before and after one dose of metyrapone during treatment with budesonide.*
*B = basal; P = after metyrapone, shaded area = mean (SD) normal concentration.*

treating asthma in children dependent on steroid treatment when given in a dose of 200 μg twice daily using a standard pressurised inhaler without a spacer.

The efficacy of BUD given twice daily is well established in the treatment of such children [6] [7] We know of only two other published studies, which report that BDP is as effective when given twice daily as it is when given four times daily (Williams H, *et al.* Abstract presented at 49th Annual Scientific Assembly Chicago 1983).[16] Our study shows that either drug can be used successfully twice daily for most asthmatic children who depend on steroid treatment.

Adrenal function was assessed by measuring 24 hour urinary excretion of THE and THF, which have been shown to be good indirect measures for cortisol excretion [11] We also measured concentrations of cortisol, 11-deoxycortisol, and ACTH in plasma before and after challenge with metyrapone. Although we have not included a group of normal controls in this study, we have taken normal values from published reports and from experience in our own laboratory [11] [14] [15] Urinary excretion THE and THF, and basal concentrations of cortisol and ACTH in plasma were found during both sets of treatments. The response of 11-deoxycortisol concentrations to a dose of metyrapone was mildly decreased in two patients during treatment with BUD and in four during treatment with BDP. These results suggest that, although safe for most patients, both drugs may moderately suppress the function of the pituitary adrenal axis when given in a dose of 200 μg twice daily

Since this study was undertaken, Law *et al*[17] have shown that nocturnal cortisol excretion rates fall according to dose in children using inhaled steroids. [7] Further studies of this type are needed before any conclusions can be reached as to the possible advantage of one or other inhaled steroid.

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# Children and mothers at clinics: who is disturbed?

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SUMMARY One hundred and eighty one white children aged 6 to 11 years who were attending medical outpatient clinics with their mothers were studied to assess the prevalence of psychological disturbance in the children, and anxiety and depression in the mothers. Teachers were also asked to assess the children independently using the Rutter scales. Mothers assessed 70 (39%) of the children as being disturbed, 20 of whom were also assessed as being disturbed by their teachers. A further 15 children were assessed as being disturbed by their teachers but not by their mothers. Thirty five (19%) of the mothers assessed themselves as anxious and two as depressed using the hospital anxiety and depression scale. Anxious and depressed mothers were significantly more likely to assess their child as being disturbed. In contrast, the teachers' assessments of the children were not affected by the mental state of the mothers. These findings confirm that mothers' perceptions of their children are modified by their own moods.

The availability of a wide range of facilities for diagnosis and treatment, and a healthy concern for the psychological wellbeing of children means that paediatrics is increasingly becoming an outpatient specialty. An assessment of the psychology of the child and the family is crucial to understanding the child and his or her illness. A detailed assessment of psychological function is hardly practicable, however, within the constraints of the usual outpatient consultation. Recent work with adults has shown that useful information may be obtained from brief questionnaires that assess anxiety and depression given to patients while they are waiting for outpatient consultations.[1]

This study was undertaken to determine the prevalence of psychiatric disturbance, which was assessed by their mothers and schoolteachers, in a sample of children attending outpatient clinics and the prevalence of anxiety and depression in the mothers, which they assessed themselves. The study also explored the correlation between the separate assessments of the children and their mothers' anxiety and depression with facts about the illness and the family.

Specific hypotheses were that maternal anxiety and depression affect mothers' perceptions of their children's disturbance, and that severity of the child's illness is more psychologically disturbing to the mother than to the child.

## Patients and methods

One hundred and eighty one white children aged 6 to 11 years who were attending medical outpatient clinics accompanied by their mothers were studied. Many of the Asian mothers attending the clinics did not have a good command of English, and so only white children were included in the study. The clinics sampled were mainly general paediatric clinics, but also some subspecialty clinics for children with diabetes, cancer, cystic fibrosis, renal problems, and enuresis. None of the clinics specifically dealt with children with emotional or psychiatric problems, nor were children selected for study because of psychological problems, the length of time immediately prior to consultation was the main factor which determined their inclusion in the study. Towards the end of the study some children with asthma and enuresis were not included because these diagnoses were already well represented in the sample.

Children and their mothers were greeted in the waiting area and invited to take part in the study while awaiting their consultation. They were told that the study aimed to find out how mothers and children feel when they attend outpatient clinics, but not about how they felt about the clinic or hospital. If both mother and child agreed to participate they were given questionnaires to fill in individually. Two mothers refused to participate in the study.

The mother was first asked to complete a short questionnaire about her marital and employment status, the number of other children in the family, and the position of the child within the family. She then completed a Rutter $A_2$ scale[2] about the child's health and behaviour, and finally completed a hospital anxiety and depression scale about herself,[1] which was prefaced by a paragraph explaining why parents' feelings may be useful in understanding the child. Concurrently the child completed a children's version of the hospital anxiety and depression scale, comprising six questions. Children aged 8 to 11 then completed the depression self rating scale for children [3] Written consent was obtained for a Rutter $B_2$ scale to be sent to the child's schoolteacher for completion.[4]

The author was present in the waiting area, usually seated next to the mother and child, and helped children to read their questions if necessary Mothers and children took between 10 and 20 minutes to complete their questionnaires.

The Rutter $A_2$ scale comprises 31 questions and statements on the child's health, habits, and behaviour over the preceding 12 months. The mother could give one of three responses to each question or statement: (a) does not apply, (b) applies somewhat; (c) certainly applies. Responses were scored 0, 1, or 2, respectively. A score of 13 or more has been found to be the best discriminator between children who are psychiatrically disturbed and those who are not.[2] The Rutter $B_2$ scale comprises 26 statements with three possible responses, which are scored like the Rutter $A_2$ scale. A score of 9 or more has been shown to discriminate best between disturbed and non-disturbed children and this was used in this study.

The hospital anxiety and depression scale, which was validated with adults attending outpatient clinics in Leeds, includes 14 statements about how the person has felt in the past week, seven of which are designed to measure depression, and seven anxiety.[1] There are four possible responses to each statement, which are scored from 0–3. A score of 11 or more on the relevant subscale indicates definite anxiety or depression, and a score of 8 to 10 mild anxiety or depression

The following information was extracted from the child's medical notes and coded for analysis age, main diagnosis, type of drug treatment, period of time attending that clinic, number of clinic attendances, previous attendance at other clinics, and previous admission to hospital. Diagnoses were grouped into 'minor', 'major', or 'very serious' depending on whether they were chronic, their degree of severity, and the mortality risk. For example, asthmatics who required regular treatment with steroids or theophyllines were classified as 'major', and other asthmatics were classified as 'minor'. Diabetes mellitus, cystic fibrosis, epilepsy, and nephrotic syndrome were classified as 'major', and all children with cancer or renal failure were classified as having 'very serious' diseases. Classification of the severity of diagnosis was made without knowledge of the psychological ratings. The $\chi^2$ test was used for initial analysis. Correlations between variables were explored further using a stepwise logistic regression analysis (BMDP statistical package) to determine which variables seemed to predict mothers' ratings of the children's disturbance.

Permission for the study was granted by the ethical committee of Leeds Eastern Health Authority, and by the director of education for Leeds City Council.

## Results

Ninety three (51%) of the children studied were boys. There was an even distribution of children across age groups: 59 (33%) were 6 to 7 years old, 59 (33%) were 8 to 9, and 63 (35%) 10 to 11. Table 1 summarises the principal diagnoses of the children studied. Diagnoses were classified as minor in 109 (60%), major in 54 (30%), and very serious in 18 (10%). Eighty seven (48%) of the children were not taking any drugs, 43 (24%) were taking sympathomimetic drugs for asthma, nine (5%) oral steroids, six (3%) insulin, six (3%) anticonvulsants, and 30 (17%) were having other forms of drug treatment

Table 1 *Diagnoses of 181 children studied*

| *Diagnosis* | *No of children* |
|---|---|
| Asthma | 41 |
| Urinary tract infections<br>Recurrent haematuria<br>Nephrotic syndrome | 33 |
| Enuresis<br>Soiling | 18 |
| Abdominal pains<br>Migraine<br>Headaches<br>Joint pains | 18 |
| Malignancy | 15 |
| Epilepsy | 8 |
| Renal failure | 7 |
| Diabetes mellitus | 6 |
| Non-malignant haematological disorders | 6 |
| Cystic fibrosis | 3 |
| Short stature | 3 |
| Others, including, inflammatory bowel disease, congenital adrenal hyperplasia, recurrent respiratory infection dizzy spells | 23 |

Twenty three (13%) of the children were attending the clinic for the first time. Of the remaining 158, 44 were attending clinic more than 10 times a year. Fifty eight (32%) had attended other outpatient clinics, and 121 (67%) had been admitted to hospital.

The mean number of children in each family was 2·5. and 75 (41%) of those in the study were the first child in their family. Of the mothers, 148 (82%) described themselves as married, 22 (12%) as divorced, one as separated, and 10 as single Forty (23%) of the children came from families in which the head of the household was unemployed. Of the parents, 72 (40%) were manually employed and 65 (36%) had other types of jobs. One mother did not understand all the questions she was required to answer, and one mother refused permission for the Rutter $B_2$ scale to be sent to her child's schoolteacher Seven (4%) of the Rutter $B_2$ assessments were not returned by the schoolteachers.

**Children's disturbance assessed by mothers and teachers.** Seventy (39% of the children were assessed as being disturbed by their mothers, and of these, 20 were also identically assessed by their teachers. An additional 15 were assessed as being disturbed by their teachers but not by their mothers. Both mothers and teachers assessed proportionately more boys than girls as being disturbed. Forty (44%) of the boys and 30 (34%) of the girls were assessed as being disturbed by their mothers. Twenty two (26%) of the boys and 13 (15%) of the girls were assessed as being disturbed by their teachers.

**Maternal anxiety and depression.** Thirty four (19%) of the mothers regarded themselves as definitely anxious and 47 (26%) as mildly anxious Two mothers felt that they were definitely depressed and 14 (8%) that they were mildly depressed. Eleven (28%) and 14 (36%) of mothers from homes where the head of the household was unemployed were definitely and mildly anxious, respectively, compared with 23 (17%) and 33 (24%) of mothers where the head of the household was employed ($p<0{\cdot}05$).

**Correlation with children's disturbance and maternal anxiety and depression.** Table 2 summarises the variables that were significantly related to children's disturbance. These variables were likely to be interrelated, so a stepwise logistic regression analysis was done to discover which variables were most predictive of children's disturbance, as assessed by their mothers. Four (maternal anxiety, maternal depression, number of clinic attendances, and family size) were found to be independently associated with the mothers' assessments of their children's disturbance. Using stepwise logistic regression analysis, only maternal anxiety ($p=0{\cdot}01$) and family size ($p=0{\cdot}04$) were significant.

**Children's disturbance and maternal anxiety or depression related to severity of child's illness.** Nine (50%) of the very seriously ill children, 20 (37%) of the children with major illnesses, and 41 (38%) of those with minor illnesses were considered to be disturbed by their mothers. None of the very seriously ill children, 14 (29%) of the children with major illnesses, and 21 (20%) of those with minor illnesses were thought to be disturbed by their teachers. Twenty eight (24%) of the children who had been previously admitted to hospital were assessed as being disturbed by their teachers, compared with seven (12%) of the children who had not been admitted ($p<0{\cdot}05$).

Six (33%) of the mothers of children with very serious illnesses were definitely anxious, compared with 10 (19%) of the mothers of children with major

Table 2 *Variables related to mothers' and teachers' assessments of children*

| | *Mothers' assessments of children (Rutter $A_2$ scale)* | | | *Teachers' assessments of children (Rutter $B_2$ scale)* | | |
|---|---|---|---|---|---|---|
| | *Disturbed* | *Not disturbed* | *p value* | *Disturbed* | *Not disturbed* | *p value* |
| Maternal anxiety: | | | | | | |
| Definitely anxious | 20 | 14 | | 6 | 28 | |
| Mildly anxious | 22 | 24 | <0·01 | 8 | 35 | NS |
| Not anxious | 28 | 70 | | 19 | 75 | |
| Maternal depression: | | | | | | |
| Definitely and mildly depressed | 10 | 6 | <0·05 | 3 | 11 | NS |
| Not depressed | 60 | 103 | | 30 | 127 | |
| Family size: | | | | | | |
| Four or more children in family | 4 | 18 | <0·05 | 8 | 14 | <0·05 |
| Three or fewer children in family | 65 | 92 | | 27 | 123 | |
| Employment of head of household | | | | | | |
| Unemployed | 19 | 21 | NS | 14 | 24 | <0·01 |
| Employed | 50 | 87 | | 19 | 112 | |

illnesses, and 18 (17%) of those with minor illnesses. Maternal depression was not related to the severity of the child's illness, one child with a very serious illness had a definitely depressed mother, the other definitely depressed mother having a child with a minor illness.

Other variables, like type of illness, drug treatment, and number of clinic attendances were not significantly related to the children's or mothers' disturbances.

## Discussion

The amount of information obtained about a patient's psychological state is necessarily limited by the time available for assessment in the outpatient clinic. It is therefore important to select appropriate methods to facilitate this. The Rutter scales are widely used, having been well validated in a community study on the Isle of Wight they detect psychiatric disturbance in children, and are more reliable for detecting disorders of conduct than affective disorders.

The prevalence of disturbance in children found in this study was similar to that found by Fitzgerald in children attending outpatient clinics in London.[5] Using the teachers' questionnaire, the rates of disturbance found in Leeds (26% among boys and 13% among girls) were similar to those found in a community survey of 10 year olds in an inner London borough (25% among boys and 13% among girls), but considerably more than the corresponding rates for children on the Isle of Wight (14% among boys and 7% among girls).[6]

There were wide discrepancies between a teacher's assessment of a child using the Rutter $B_2$ scale, and a parent's assessment of the same child using the Rutter $A_2$ scale, and it was assumed that this was because mothers and teachers saw the children in different environments Evidence from community studies[7] [8] and studies from psychiatric clinics,[9] [10] however. suggest that the mothers' perceptions are influenced by their own affective disorders, and that these affect the way in which they assess the children's behaviour.

A pilot study in paediatric outpatient clinics in Leeds showed that mothers' mood disorders might be influencing their assessments of their children's behaviour. The first hypothesis of this study was, therefore, that maternal anxiety and depression would affect mothers' perceptions of their children's level of disturbance as measured by the Rutter $A_2$ scale. Anxiety and depression in the mothers was measured by the hospital anxiety and depression scale This scale has been validated locally, is easy to complete, and restricts the concept of depression almost entirely to 'anhedonia' (an inability to experience pleasure) The prevalence of maternal anxiety (19%) was much greater than that of maternal depression (two mothers), presumably because of the more limited definition of depression implicit in this scale.

Maternal anxiety was significantly related to the likelihood of a child being considered to be disturbed by the mother and, using a stepwise logistic regression analysis, maternal anxiety proved the most important variable in predicting the mothers' assessments of their children's disturbances. This may be a genuine effect of anxiety on the mother's perception of the child, or it may be that disturbed children make their mothers anxious, or that a disturbed home background affects both mothers and children. While the latter hypotheses may be partly true, the fact that there was no increased likelihood of children with anxious mothers being seen as disturbed by their teachers strongly supports the hypothesis that maternal anxiety affects the mothers' perceptions of their children's disturbance

There was a similar, but less important association between maternal depression and mothers' assessments of their children's disturbance. Other studies have shown that depression appreciably affects mothers' assessments of their children,[8] [9] and influences their use of medical facilities for their children.[11]

Table 2 shows that there are noticeable differences between mothers' and teachers' assessments of children's disturbance. The second most important variable affecting mothers' assessments was the size of the family, children from large families (four or more children) being significantly less likely to be disturbed according to their mothers There was no evidence, however, that only children were particularly likely to be thought of as disturbed by their mothers Conversely, teachers were more likely to regard children from large families as disturbed

Unemployment of the head of the household significantly affected the teachers' assessments of the children, but not those of the mothers. This may be because antisocial and disruptive behaviour is more likely to manifest itself at school

It seems that if a mother is asked to assess her child's disturbance using the Rutter $A_2$ scale, that assessment will be subjective, and influenced by the mother's own mental state. Rutter *et al*[2] recommend that the teachers' and mothers' scales should be analysed together but, although the scales provide more information when used in this way, obtaining a teacher's assessment before an outpatient consultation is not usually practicable.

Severity of illness judged by a doctor had little effect on mothers' assessments of their children's disturbance using the Rutter $A_2$ scale although children with very serious illnesses were slightly more likely to be assessed as being disturbed by their mothers. Teachers, however, considered none of the very seriously ill children to be disturbed, possibly because teachers make allowances for disturbed behaviour if they know that a child is likely to die of his or her illness

There was an insignificant trend for mothers of children with more serious illnesses to be more anxious. As there were only two definitely depressed mothers, no association could be found between maternal depression and severity of the child's illness. There was, therefore, some confirmation that mothers suffer more psychological disturbance as a result of the severity of their child's illness than do the children themselves.

This study has shown that the mothers' own moods have an important influence on their assessments of their children's behaviour. It may be unwise to assume that teachers are any more objective than mothers in their assessments of children, but it is clear that individual results from Rutter scales should be interpreted with caution. Self assessment scales for anxiety and depression were acceptable to mothers, and are useful to the clinician. Rapid scoring of the hospital anxiety and depression scale allows information about the mother's mental state to be made available during subsequent consultation, which should facilitate discussion about psychological factors related to a child's illness

Measures of a child's psychological disturbance that depend on behaviour observed by adults have some value, but may be less informative than more direct assessments of the child's affective state. There are many problems to be overcome in finding a reliable measure of children's affective disorders, particularly within the constraints of an outpatient visit.[12] In the absence of other suitable measures to make it easier to understand the whole child, paediatricians should continue to listen to the children themselves.

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# Expiratory muscle activity in preterm babies

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SUMMARY The activity of the right external abdominal oblique muscle, in relation to respiration, in newborn babies from 25 to 34 weeks' gestation was studied, using surface electrodes. Babies without respiratory difficulties showed no activity associated with respiration in these muscles. Grunting babies with respiratory disease showed pronounced activity during expiration. This activity continued when the babies were endotracheally intubated; if the babies were ventilated it sometimes disturbed the tidal ventilation delivered by the machines. When the baby expired during a ventilator inflation, so that gas came up the endotracheal tube against the inflating pressure, the abdominal oblique muscles contracted in 98% of the breaths.

In adults certain muscles of the abdominal wall are active during forced expiratory manoeuvres.[1] What knowledge exists on the activity of these muscles in preterm babies suggests that they may be active during expiration in the presence of respiratory disease.[2] Previous work from our department has shown that most babies on ventilators make spontaneous respiratory efforts.[3] When a ventilated baby breathes out during a ventilator inflation and disturbs the tidal volume delivered by that inflation, it increases the risk of pneumothorax.[4] This pattern of interaction between the baby and the ventilator was termed 'active expiration', because it was thought that expiratory muscle activity played a part.[4] This suggestion has been questioned.[5]

To investigate the activity of the expiratory muscles we developed a technique of abdominal muscle electromyography, which we have used to study newborn babies in an attempt to answer the following questions: do preterm babies have expiratory muscle activity, and if they do, under what circumstances does it occur?

We chose to study the external abdominal oblique muscle. The fibres arise from the lower eight ribs, passing anteriorly and caudally to the anterior half of the iliac crest and a fibrous aponeurosis which continues to the midline Contraction of the muscles compresses the abdominal contents and pushes up the diaphragm; it also draws the lower ribs downwards and medially These muscles have been shown to contract during active expiratory efforts in adults but little is known of their activity in the preterm baby [1]

## Methods

Three groups of babies were studied during the first few days of life· six well preterm babies (28 to 32 weeks' gestation, mean 30 weeks) with no respiratory illness; five babies with the respiratory distress syndrome who were grunting, and 34 babies with respiratory distress syndrome who were intubated and ventilated (25 to 34 weeks' gestation, mean 29 weeks). The babies on ventilators were selected at random from the intensive care nursery over six months. They were studied once during the first week of life. Only babies who could be seen to be making respiratory efforts while being ventilated were studied Babies receiving neuromuscular blocking agents were not selected, nor were those termed clinically 'unstable'.

The babies were studied in their cots or incubators, in the supine position, and at a time when they were quiet, making no gross body movements. No further assessment of arousal state was made All, apart from the six well babies, were studied in the intensive care section of the neonatal unit, where there are many sources of electrical interference.

Full details of the technique for recording the electromyogram (EMG) potentials from the external abdominal oblique muscle are reported elsewhere.[6] We used standard self-adhesive neonatal electrocardiogram electrodes placed over the right external abdominal oblique muscle, parallel to the direction of the muscle fibres and along a line perpendicular to the electrocardiogram vector at this point. This results in the best EMG signal with least interference from the electrocardiogram. Signal filtering was kept to the minimum consistent with obtaining interpretable signals, and consisted of 50 Hz notch filtering, a low cut off filter (set between 0·3 and 1·0 Hz) to reduce movement artefacts, and a high cut off filter (set between 300 and 1000 Hz) to reduce interference from electrical apparatus (particularly electrocardiogram monitors). The EMG signals were compared with the babies respiratory cycles, which were recorded from a pneumotachograph and an abdominal respiration monitor.

The well babies and those who were grunting with respiratory distress syndrome had masks that incorporated the pneumotachograph, which was placed gently over their faces and from which gas flow and tidal volume could be recorded. A respiration monitor (Graseby-Dynamics MR10) was placed on the abdomen. The signals were recorded on a polygraph. Recordings of the EMG signal were also made without the face mask to determine whether its presence influenced external abdominal oblique muscle activity. If no muscle activity was seen on the EMG signal then a loud handclap was used to stimulate movement in the baby; activity on the EMG trace then confirmed that the apparatus was responding correctly. The six well babies were each studied for at least 30 minutes and the grunting babies for at least 10 minutes. If the grunting babies had been receiving oxygen this was continued during the study.

The thirty four babies with respiratory distress syndrome who were intubated and ventilated were studied in the same way as the other two groups, except that the pneumotachograph was placed in series with the endotracheal tube. Two recordings were performed on each of these babies: firstly a 30 second period during which the baby breathed spontaneously with continuous positive airway pressure (CPAP), and then a period of about 100 ventilator cycles while the baby was receiving intermittent positive pressure ventilation (IPPV). The ventilator settings were those selected by the clinical team and the level of CPAP used for the period of spontaneous breathing was the same as the end pressure during IPPV. A period without the pneumotachograph in place was also observed to determine if its presence might influence the activity of the external abdominal oblique muscle. The respiration monitor used on the upper abdomens of these babies showed spontaneous respiratory activity with little or no interference from mechanical ventilation.

In each case the calibration of zero flow and volume detection by the monitoring system (pneumotachograph, differential pressure transducer and electronic integrator) was checked immediately before and after the observation period. In no case had there been any drift in the baselines.

## Results

Comparison of the traces with and without the pneumotachograph or the face mask in place showed no differences in activity of the external abdominal oblique muscle that could be attributed to the presence of these devices.

**The well babies.** During observation, there was no activity of the external abdominal oblique muscles related to respiration. Activity in these muscles during trunk movements showed that this was not a failure of the recording technique (Fig 1). Some babies responded to the siting or removal of the face mask by crying, and there was clear evidence of external abdominal oblique muscle activity during the expiratory cry, but not during the intake of breath between cries.

**The grunting babies.** When audibly grunting, all babies showed noticeable activity in the external abdominal oblique muscles. This activity coincided with the prolonged expiratory phase that is seen during grunting and which was absent during the inspiratory phase (Fig. 2).

**The intubated babies.** Recordings from 13 of the 34 babies studied were not used because electrical interference on the traces prevented us from confidently detecting the presence of external abdominal oblique muscle activity. The masking from excessive interference was evident at the same levels

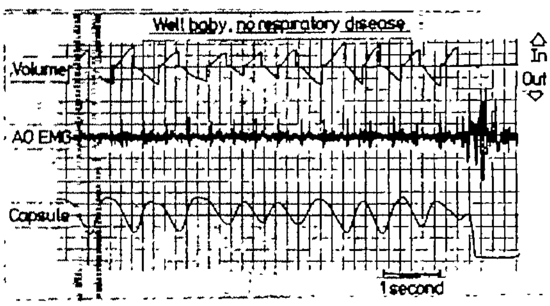

Fig 1 *Respiratory activity in a healthy baby, breathing spontaneously. Volume=tidal volume, from face-mask pneumotachograph, Capsule=signal from pneumatic respiration monitor, AO EMG=abdominal oblique EMG signal, there is no obvious muscle activity in association with respiration, electrocardiogram potentials are visible, and episode to the right of record is a 'wriggle' which shows that the EMG system is working*

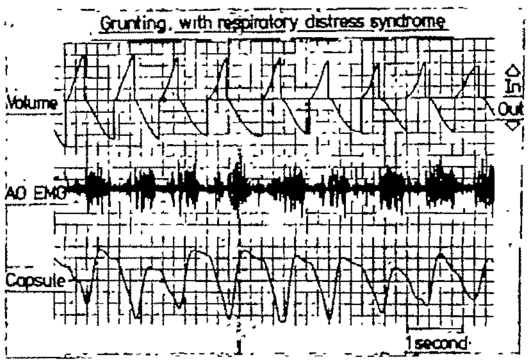

Fig 2 *Respiratory activity in a grunting baby with respiratory distress syndrome Burst of activity in the abdominal oblique muscles is visible during each expiration.*

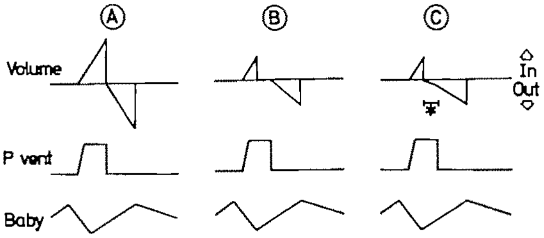

Fig. 3 *Diagrammatic respresentation of the effects of expiration by the baby during a ventilator inflation. Top trace tidal volume (gas flow down endotracheal tube shown as upward deflections and gas flow up tube as downward deflections. Middle trace. ventilator circuit pressure Bottom trace respiratory efforts (inspiration downward deflection, expiration upward) A baby's expiration does not influence tidal volume delivered by ventilator. B: baby's expiration has reduced tidal volume delivered. C: tidal volume is reduced and in addition there is gas flow up endotracheal tube against inflation pressure (during the period marked *)*

of signal amplification as the traces which were used The results were taken from the remaining 21 babies

During the 30 second period of breathing with CPAP, some external abdominal oblique muscle activity during expiration was observed in all the babies. Although not quantified in any way, the degree of activity in babies on higher CPAP seemed to be greater than those on lower CPAP. In 10 babies we performed a further 30 second observation, beginning with a CPAP of 8 cm $H_2O$ and reducing to zero after 15 seconds. In six of these babies the respiratory pattern changed to a faster rate, with either the disappearance of, or a noticeable reduction in, external abdominal oblique muscle activity when lower CPAP was used.

When the babies were receiving IPPV, external abdominal oblique muscle activity was still seen in relation to the baby's spontaneous respiratory cycles, and did not seem to be specifically stimulated by ventilator inflations. If a ventilator inflation coincided with spontaneous expiration there were three possible effects on the tidal volume delivered to the baby by the ventilator. Firstly the baby's expiration had no affect on the tidal volume (Fig. 3a), secondly, the tidal volume was reduced compared with an unaffected inflation (Fig. 3b), and finally, the baby's expiratory efforts reduced the tidal volume delivered and in addition, forced gas up the endotracheal tube against the inflating pressure (Fig. 3c). The first two patterns were often seen in all the babies in the absence of external abdominal oblique muscle activity. The third pattern is of particular interest. We determined how commonly it was observed (Fig. 4).

We analysed 2150 ventilator cycles from the 21 babies. Eighteen babies (86%) had episodes during

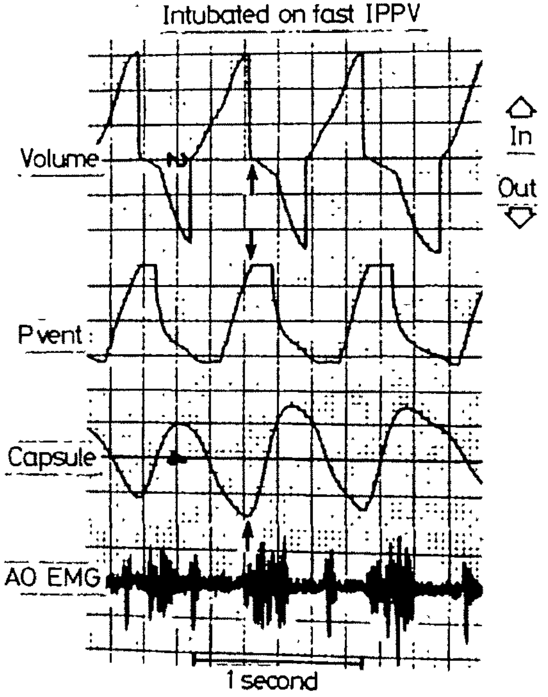

Fig. 4 *Respiratory activity in a ventilated baby with respiratory distress syndrome. This shows pattern schematically represented in figure 3c Signals are as shown in figures 1 and 2, with the addition of ventilator circuit pressure (P VENT). During each ventilator cycle baby moves into an expiratory phase at a point when ventilator is reaching peak inflation pressure (arrows). Small amount of gas is forced up endotracheal tube against the inflation pressure Note burst of abdominal oblique activity*

which part of the ventilator inflation coincided with the baby's expiratory phase and gas flowed up the endotracheal tube against the ventilator inflation pressure. Overall, this pattern was seen during 441 (21%) of the 2150 ventilator inflations, and in individual babies its occurrence varied from 0 to 88% of the analysed breaths. Of these 441 episodes of expiratory flow during ventilator inflation, 432 (98%) were associated with a detectable burst of activity in the external abdominal oblique muscles.

## Discussion

We have shown that there is respiratory activity of the external abdominal oblique muscles in preterm babies. This activity coincides with expiration and it seems reasonable to conclude that, as in adults these muscles may provide an active component to expiration. Showing that the expiratory muscles are active by electromyography, however, does not quantify their contribution to expiratory forces when compared with passive recoil alone; it only shows they are contracting.

Well preterm babies do not show expiratory muscle activity except during trunk movement or crying. Those with respiratory disease use their expiratory muscles when grunting; this activity is often present when the baby is intubated and breathing spontaneously with CPAP, and also when undergoing mechanical ventilation.

The role that active expiration might have in babies with respiratory disease is open to speculation. If expiratory gas flow is powered by abdominal muscle contraction in addition to the forces of passive recoil, then the flow rate would be expected to be high and the duration of expiration short. In non-intubated babies with respiratory distress syndrome who contract their abdominal muscles during expiration, this is not the case. Expiratory flow rate is low and the duration of expiration is prolonged because laryngeal adduction retards expiratory gas flow, which in turn prolongs expiration.[8] The grunt is produced by gas being forced through the partially closed larynx. This may help preserve lung volume in conditions where it tends to be low and may also help force gas into unexpanded regions of the lung. The insertion of an open ended endotracheal tube prevents laryngeal adduction and deprives the baby of this mechanism to maintain lung volume. Deterioration of oxygenation usually ensues.[2] We have observed that an intubated baby breathing against 8 cm $H_2O$ of CPAP behaves like a grunting baby, with a prolonged expiratory time and a lot of expiratory muscle activity. If CPAP is reduced to zero some of these babies switch to a fast respiratory rate with a short expiratory duration and very little expiratory muscle activity. This may be a different mechanism for preserving lung volume. A short expiratory time without any active expiratory effort may give insufficient time for complete lung emptying (taking time constants into consideration) and thus result in a higher functional residual capacity. This dynamic increase in lung volume from 'inapparent PEEP' could be beneficial in these circumstances.

The expiratory activity of ventilated babies can affect the tidal volume delivered by a ventilator inflation. In particular, gas being forced up the endotracheal tube against the inflation pressure is almost consistently associated with abdominal muscle contraction.

Can preterm babies contract their expiratory muscles sufficiently to overcome the ventilator inflation pressure, which in some circumstances may be more than 30 cm $H_2O$? In the ventilated baby who is also breathing spontaneously the forces expanding the lungs comprise the negative pressure generated during inspiration by the baby and the positive pressure applied by the ventilator. At the peak of any given tidal inflation these forces will be balanced by the elastic recoil of the lungs and chest wall. At this point, either the subtraction of the baby's inspiratory efforts or the addition of an expiratory force—that is, contraction of the expiratory muscles or both—may cause expiratory forces to exceed inspiratory forces which results in gas being forced up the endotracheal tube against peak inflation pressure. Interestingly expiratory muscle activity was almost always seen in these babies. The interaction of these forces is complex and may well vary from breath to breath.

If a force is applied to the chest by the expiratory muscles during ventilator inflation high intrapulmonary pressures may result. Distribution of intrathoracic pressure and lung compliance is not uniform, so gas may be forced into the more compliant compartments (particularly the larger airways), leading to rupture.[9] This may explain the association of pneumothorax with this particular pattern of baby-ventilator interaction.

Newborn babies with respiratory disease often contract their abdominal muscles during expiration. This can affect the efficacy of treatment using ventilators and add to its complications. The spontaneous respiratory activity of ventilated babies is an important component of ventilation and should not be ignored.

We thank Professor J A Davis, Dr N R C Roberton and Dr G Gandy for their encouragement and advice, and the nursing staff of the neonatal unit at the Rosie Maternity Hospital. This work is funded by the University of Cambridge Baby Research Fund.

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# Fifty years ago

## Iron deficiency anaemia of late infancy

*H W Fullerton (Aberdeen)—Arch Dis Child* 1937;**12**:91–110

This was the first British assessment of the frequency of nutritional anaemia in infancy to follow Dr Helen Mackay's extensive studies in London in 1933 Haemoglobin estimations by the Haldane method were made in 789 infants of all ages up to 23 months The incidence of severe anaemia increased towards the end of the first year and continued to be high throughout the second year. Haemoglobin concentrations <80% (11 8 g/dl) were found in 87% of 298 infants of the "poorer classes" between the ages of 9 and 23 months Fullerton concluded that the common anaemia of late infancy was due mainly to iron deficiency, which was dependent on low birth weight, prolonged milk (especially artificial) feeding, and infective illnesses. Maternal iron deficiency was regarded as having little or no influence on the development of anaemia in infancy. Analysis of the quantitative aspects of iron deficiency led to the conclusion that a deficient intake of iron during the first nine months did not have a pronounced effect on the haemoglobin concentration but that a deficient iron intake would become of increasing importance as growth continued Fullerton saw no need for drastic dietary revisions but he did recommend the prescription of medicinal iron from the age of 3 months to all infants of birth weight less than 7 lb (3200g) and to all who were artificially fed

**Comment.** Iron deficiency anaemia is less common today (32% of Glasgow children between 6 and 24 months) Infants with very severe anaemia and cardiomegaly complicated by infection and requiring emergency blood transfusion were not uncommon before the second world war They are almost unknown today. In the 1930s mixed feeding was not commonly introduced before the age of 9 months and the present practice of starting mixed feeding, including iron fortified cereals, between the ages of 3 and 6 months probably has a preventive role A case can still be made, however, for testing infants aged 9 to 12 months, especially in underprivileged families, and prescribing medicinal iron to those found to have anaemia The need for iron supplements in premature babies is well recognised.

(Harold Fullerton was not a paediatrician but a general physician with a special interest in haematology. He later became Professor of Medicine in the University of Aberdeen )

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# Energy and nitrogen balances in very low birthweight infants

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SUMMARY Energy and nitrogen balances were performed in 12 very low birthweight infants fed on either human milk or on a preterm formula. Energy and nitrogen retention were significantly higher in those given the formula feed ($p<0·05$). Highly significant correlations were found between nitrogen intake and nitrogen retention and between energy retention and nitrogen retention ($p<0·001$). Multiple regression analysis failed to show any effect of energy retention on the correlation between nitrogen intake and nitrogen retention in babies fed on human milk. Protein deficiency seems to be the most likely explanation of poor growth in infants fed on human milk.

During the past few years many studies of metabolic balance in preterm infants fed on expressed human milk or preterm formulas have been reported, but few have concerned very low birthweight infants (<1500 g).[1 2] These infants are the most vulnerable to nutritional deficiencies, the most immature in metabolic development, and the most likely to suffer impaired growth and the other sequelae of poor nutrition.

This study aimed to compare the results of metabolic balance studies and to examine the association between energy balance and nitrogen balance in two groups of such infants, fed either human milk or a preterm formula.

## Patients and methods

The 12 babies studied were all premature infants admitted to the neonatal unit at St George's Hospital. They all weighed less than 1500 g, both at birth and on entry to the study, were well, and gaining weight. Some of them had already had metabolic balance studies.[3]

Table 1 gives details of their birth weight and gestational age: none had any congenital abnormality. They were in air mode controlled (not servo controlled) incubators during the study. Informed consent was obtained from the parents, and the studies were approved by the hospital ethical committee.

Three day balances were performed on 23 occasions in 12 very low birthweight infants. Eight infants were fed on human milk (six from their own mothers, unheated, and two from the milk bank, pasteurised), and four were fed on a preterm formula (Pre-Aptamil, Milupa Ltd), the composition of which is given in Table 2. A sample of human milk used for each balance was taken for analysis. Pre-Aptamil of the same lot (No 222104) was also analysed, but as the composition of milk is constant we did not analyse it more than once. The volume taken at each feed was measured using a 20 ml syringe.

Balances were measured over three days, a carmine marker being given at the beginning and

Table 1 *Details of infants studied*

| | *Human milk 15 balances mean (SD)* | *Pre-Aptamil 8 balances mean (SD)* |
|---|---|---|
| Birth weight (g) | 1016 (235) | 1133 (164) |
| Gestational age (weeks) | 28·4 (2·8) | 28·5 (1·7) |
| Age at the beginning of balance (days) | 31 (29) | 17 (10) |
| Weight at the beginning of balance (g) | 1243 (218) | 1258 (108) |

Table 2 *Composition of 100 ml Pre-Aptamil*

| | |
|---|---|
| Energy | 309 kJ |
| Protein | 2·1 g |
| Lactalbumin casein | 48 52 |
| Fat | 3·6 g |
| Fat blend | Vegetable oils + butter fat |
| Carbohydrate (lactose) | 8·7 g |
| Osmolality | 350 mOsm/kg |

(1 kcal=4·184 kJ)

end of each study period All stools passed during the period were collected in nappy liners and immediately frozen at −20°C. They were later weighed, freeze dried, weighed again, homogenised, and analysed for energy and for nitrogen balances using the bomb calorimeter,[4] and the Kjeldahl technique with the Kjeltec apparatus,[5] respectively

Urine was collected in nitrogen free disposable nappies which had been weighed; they were sealed in plastic containers after each change, and immediately frozen at −20°C. The nappies were subsequently weighed again to measure the volume of urine, and then washed in a known volume of water. After filtering aliquots were freeze dried and analysed for energy and nitrogen balances.[6] As stools contain some water that will contaminate the nappy, this method does not separate urine and stools completely

All infants were weighed daily on a calibrated Marsden spring balance (Marsden Weighing Machines, London), accurate to within 5 g. Weight gain, expressed as g/kg/day, was estimated over 10 days which included the three days of the study

Retention of energy or nitrogen was defined as energy or nitrogen intake (kcal/kg or mg/kg) minus (faecal plus urinary energy or nitrogen (kcal/kg or mg/kg)), expressed as a retention rate in kcal or mg/kg. The correlations between nitrogen intake and nitrogen retention, and between energy retention and nitrogen retention, were calculated using the methods of least squares and linear regression analysis. The significance of the difference between the arithmetic means was calculated using Student's *t* test

## Results

Table 3 shows the intake, output, and balance and growth measurements made during the study in the two groups of infants. There were no significant differences between the volumes of feed/kg given daily, hence energy intake was higher in the group fed on Pre-Aptamil than in the group fed on human milk, because the formula has a higher energy density; the energy content of Pre-Aptamil was 81 kcal/dl and the mean (SD) energy content of human milk 64 (9) kcal/dl. The energy retention was significantly higher in the infants fed Pre-Aptamil ($p<0·05$, Student's *t* test).

The mean (SD) nitrogen content of human milk was 242 (46) mg/dl, and that of Pre-Aptamil 329 (8) mg/dl. The infants fed human milk received an average of 452 mg of nitrogen/kg/day, corresponding to a net protein intake of 2·8 g/kg/day. Those fed Pre-Aptamil received an average of 6·6 mg nitrogen/kg/day, corresponding to a net protein intake of 3·8 g/kg/day. Mean nitrogen retention was significantly higher in infants fed Pre-Aptamil.

Table 3 *Balance data*

| | *Human milk (Mean SD) (8 infants, 15 balances)* | *Pre-Aptamil (Mean SD) (4 infants, 8 balances)* |
|---|---|---|
| Milk intake (ml/kg/day) | 184 (15) | 187 (17) NS |
| Energy intake (kcal/kg/day) | 120 (21) | 149 (12) p=0·0018 |
| Faecal + urinary energy (kcal/kg/day) | 23 (12) | 32 (16) NS |
| Energy retention (kcal/kg/day) | 97 (21) | 117 (17) p=0·03 |
| Energy retention (% intake) | 81 (10) | 79 (10) NS |
| Nitrogen intake (mg/kg/day) | 452 (92) | 606 (41) p=0·0002 |
| Faecal + urinary nitrogen (mg/kg/day) | 161 (62) | 229 (55) p=0·017 |
| Nitrogen retention (mg/Kg/day) | 297 (64) | 377 (62) p=0·009 |
| Nitrogen retention (% intake) | 66 (10) | 62 (9) NS |
| Weight gain (g/Kg/day) | 14 (6) | 17 (6) p=0·03 |

The net nitrogen use (nitrogen retention/nitrogen intake) was 66 (10) in infants fed on human milk, and 62 (9) in those fed Pre-Aptamil. There were no significant differences between the groups. Positive correlations, which were both highly significant, were found between nitrogen retention and nitrogen intake ($r=0·76$, $p<0·001$), and between nitrogen retention and energy retention ($r=0·68$, $p<0·001$) (Figure).

Using multiple regression analysis, we found that energy retention did not affect the correlation between nitrogen intake and nitrogen retention, either with human milk or with the formula, or when using the combined data.

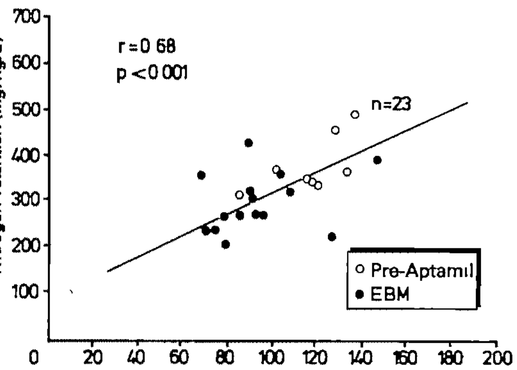

Figure *Relation between metabolisable energy and nitrogen retention in very low birthweight infants fed on Pre-Aptamil and expressed breast milk (EBM).*

Mean (SD) weight gain was significantly lower in those infants fed human milk than in those fed Pre-Aptamil being 14 (6) and 17 (6) g/kg/day, respectively (p=0·03).

## Discussion

The aim of this study was to quantify energy and nitrogen retention and the effect of energy retention on nitrogen balance in very low birthweight infants fed either human milk or a preterm formula.

The mean rate of nitrogen retention in infants fed the formula feed was 377 mg/kg/day, which is similar to the fetal accumulation rate of nitrogen between 28 and 32 weeks of gestation (about 350 mg/kg/day).[7 8] The infants fed human milk retained only about three quarters of this amount, the difference being explained by their lower nitrogen intake. The range of nitrogen intake seen in this study (337–678 mg/kg/day) corresponded to a protein intake of 2·1–4·2 g/kg/day, and there was a positive linear correlation between the amount of retained nitrogen and nitrogen intake.

Energy retention was also higher in infants fed Pre-Aptamil. This, together with the higher nitrogen retention, explains their significantly greater weight gain. The differences observed between the nitrogen and energy balances in the two groups cannot be attributed to the groups being studied at different ages; the group fed Pre-Aptamil showed higher energy and nitrogen retention despite being studied earlier (although not significantly so) than the other group.

We found a positive linear correlation between nitrogen retention and energy retention (Figure). Nitrogen balance in adults is quickly affected by the amount of energy in the diet, and several studies in low birthweight infants have shown that correction of steatorrhoea, or increased energy intake, may improve nitrogen retention;[9 10] data are, however, lacking for very low birthweight infants.

In the present study we did not change the energy:nitrogen ratio of human milk, which varied considerably. Our multiple regression analysis of data from babies fed human milk shows that the most important factor affecting nitrogen retention is nitrogen intake. This conclusion does not apply to the group fed Pre-Aptamil because the protein:energy ratio was constant and so the data could not be analysed. Our data, therefore, confirm recent observations of better weight gain in infants fed with human milk supplemented with protein compared with those whose milk was supplemented only with energy in the form of medium chain triglycerides.[11]

The energy in unpasteurised expressed breast milk and in modern preterm formulas is generally quite well absorbed by very low birthweight infants,[1 5 12] and it may be that energy is not always the limiting factor in growth that it was thought to be. It may become so, however, in infants with abnormally high energy expenditure, infection, or very poor absorption, but in healthy infants of very low birthweight, protein deficiency now seems to be the most likely cause of poor growth in nurseries that promote feeding with human milk. Consideration should be given to methods of estimation of the protein content of feeds, and to appropriate protein supplementation where necessary.

We thank Cara Kepson for technical assistance and the staff of the special care baby unit for their cooperation.

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# Comparison of weight:height ratio and arm circumference in assessment of acute malnutrition

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SUMMARY Doctors working in famine relief commonly use the weight:height ratio and the circumference of the mid-upper arm to assess the nutritional state of children under 5. Threshold values indicating moderate and severe malnutrition are usually taken as 80% and 70%, respectively, of the expected weight:height ratio and arm circumferences of 13·5 cm and 12·5 cm, respectively. A study of 1260 children aged 1–5 showed that the thresholds of these two variables yielded significantly different proportions of children with malnutrition, the proportion being much larger when arm circumference was used as the criterion. Adjusting the thresholds would result in closer correspondence between the two variables.

When working to relieve famine doctors have to screen large numbers of children as quickly as possible to assess their nutritional state. Two screening methods are commonly used: the weight:height ratio and measurement of arm circumference.[1–6] Both measurements are relatively independent of age, sex, and race. Arm circumference is a measure of the lean body mass, whereas the weight:height ratio indicates the extent of acute malnutrition; each, therefore, measures a different aspect of nutritional state. This study assessed the discrepancy that may arise when both measurements are used.

The weight:height ratio expresses a child's weight as the percentage of the expected weight for the child's height. It is usual to accept 80% of the reference median as the threshold of malnutrition. A ratio of 70–80% indicates moderate malnutrition and one of less than 70% indicates severe malnutrition.[1 2] Arm circumference increases rapidly in the first year of life[3] but then remains fairly constant between the ages of 1 and 5 years.[4] In well nourished children aged 1–5 the accepted normal is 16 cm. An arm circumference of 13 5 cm is commonly accepted as the threshold indicating malnutrition. If the circumference is between 12·5 and 13·5 cm the child is considered to be moderately malnourished, and measurements below 12·5 cm indicate severe malnutrition.[5–6] Thus in any child or population a weight:height ratio of 80% should be equivalent to an arm circumference of 13·5 cm and a ratio of 70% should be equivalent to an arm circumference of 12·5 cm. Feeding centres are usually established in areas where a fifth of children under 5 are malnourished, and any difference between the two indices of malnutrition could lead to difficulty in deciding whether to start relief

A study was carried out by Lintjørn in 1985 of 115 children in southern Ethiopia, which showed a large difference between the two methods.[7] We carried out a similar study of a much larger group of children in northern Ethiopia.

## Patients and methods

We carried out a nutritional survey of 1260 children aged 1–5 in the province of Wollo, northern Ethiopia Weight:height ratio and arm circumference were recorded for each child with Salter scales, wooden length boards, and paper tape-measures. For the ratio the expected weight for a given height was taken from the median of the World Health Organisation standards. The threshold for moderate malnutrition was taken as a weight·height ratio of less than 80% and an arm circumference of less than 13·5 cm, and for severe malnutrition the figures were less than 70% and less than 12·5 cm, respectively.

The $\chi^2$ test was used to test the significance of differences between the proportions of children in each nutritional group as assessed by the two measurements.

## Results

Comparison of the weight:height ratios and arm circumferences showed good correlation (r=0·53)

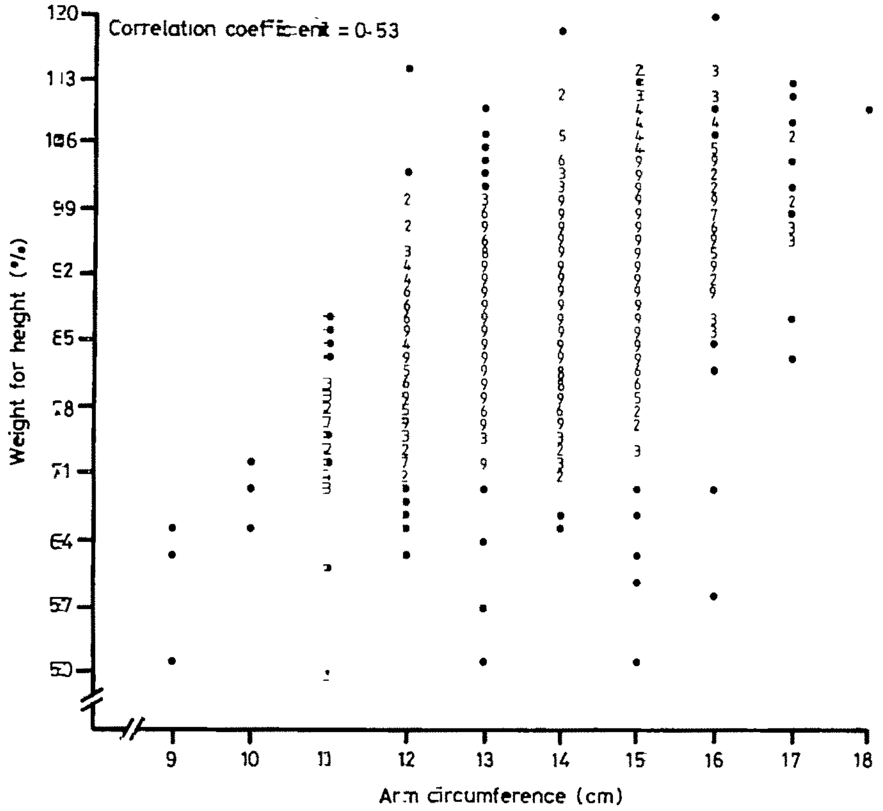

Figure *Scattergram showing correlation between weight height ratio and arm circumference in defining nutritional impairment Each dot indicates one child, while figures indicate total numbers of children at each point*

between them in defining nutritional impairment (Figure); analysis of variance showed a significant linear trend. The accepted thresholds indicating malnutrition, however, did not correspond Of the 1260 children, 168 (13%) were diagnosed as malnourished from their weight:height ratio compared with 433 (34%) from their arm circumference. This difference was highly significant (p<0·001).

Table 1 shows the numbers of children classified by the two methods as having moderate and severe malnutrition. The differences between the methods were highly significant (p<0·0001 in both cases).

Table 1 *Number (percentage) of children in each category of malnutrition*

| *Malnutrition* | *Arm circumference* | *Weight height ratio* |
|---|---|---|
| Moderate | 264 (21) | 144 (11) |
| Severe | 169 (13) | 24 (2) |
| Total | 433 (34) | 168 (13) |

Table 2 *Diagnostic agreement between weight height ratios and arm circumference measurements using currently accepted limits*

| *Arm circumference (cm)* | *Weight height ratio* | | | *Total (%)* |
|---|---|---|---|---|
| | *<70* | *70–79* | *>80* | |
| <12 5 | 12 | 63 | 94 | 169 (13) |
| 12 5–13 5 | 4 | 40 | 220 | 264 (21) |
| >13 5 | 8 | 41 | 778 | 827 (66) |
| Total (%) | 24 (2) | 144 (11) | 1092 (37) | 1260 (100) |

Table 2 presents the figures differently and shows that 830 (66%) of the children were diagnosed as having the same degree of malnutrition by both methods.

## Discussion

This study shows that there is a highly significant linear correlation between the weight:height ratio and arm circumference for all degrees of mal-

Table 3 *Diagnostic agreement between weight·height ratios and arm circumference measurements using recommended limits*

| *Arm circumference (cm)* | *Weight height ratio* | | | *Total (%)* |
|---|---|---|---|---|
| | *<70* | *70–79* | *>80* | |
| <12·5 | 8 | 22 | 9 | 39 (3) |
| 12·5–13·5 | 4 | 41 | 85 | 130 (10) |
| >13·5 | 12 | 81 | 998 | 1091 (87) |
| Total (%) | 24 (2) | 144 (11) | 1092 (87) | 1260 (100) |

nutrition. We found, however, that the thresholds taken as indicating moderate and severe malnourishment yielded significantly different numbers of children, such that there would be disagreement about whether relief was necessary. The difference may be explained by the fact that the two screening methods measure different aspects of nutritional state, but it is nevertheless important that cut off values correspond.

We recommend that the cut off values be adjusted so that they correspond more closely. If an arm circumference of 12·5 cm was taken to be equivalent to a weight:height ratio of 80%, and a measurement of 11·5 cm was taken to be equivalent to 70%, the correlation would be greatly improved, so that 82% of the values would correspond (Table 3) instead of the 66% correspondence with the currently accepted limits.

I thank Professor D C Morley and Dr Z Ebrahim for their help in producing this paper

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# *Short reports*

## Whole blood assay of theophylline concentrations using immunochromatographic stick at the bedside

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SUMMARY Blood was collected from 77 patients for estimation of theophylline concentration by whole blood assay using an immunochromatographic stick (Acculevel, Syva UK, Maidenhead, Berkshire). Results were validated by high performance liquid chromatography (HPLC). The stick method was rapid, reliable, required no technical expertise, and produced results equivalent to those obtained from assay from HPLC.

Methylxanthines are commonly used in the treatment of asthma. The necessity for monitoring theophylline concentrations in serum has been emphasised by many authors, who have reported wide variations in the pharmacokinetics of theophylline not only among patients but also within the same patient.[1 2] Theophylline concentrations measured in saliva have been shown to be unreliable.[3]

Various techniques are used to measure theophylline concentrations in serum. The purpose of this study was to compare results obtained by high performance liquid chromatography (HPLC) with those of a simple stick assay carried out at the bedside.

### Patients and methods

Seventy seven patients, aged from 1 to 14 years, were studied at two hospitals. They all received theophylline orally or aminophylline intravenously. Informed consent was obtained from the parents.

A sample of 1·0 ml of whole blood was obtained by venepuncture, and 12 µl were aspirated into a graduated pipette. The serum was separated from the remaining sample and assayed by HPLC. The stick assay was performed by adding 12 µl of whole blood from the graduated micropipette to reagent 1, which contained 1 ml conjugate of glucose oxidase, horseradish peroxidase labelled theophylline, and sheep antiserum in 0·1 M phosphate buffered saline at pH 7·0. The cassette contained chromatography paper impregnated with mouse monoclonal antibodies to theophylline. The patient's theophylline concentration and enzyme labelled theophylline rose together by capillary action, binding to the immobilised antibody sites on the cassette chromatography paper, with glucose oxidase saturating the remaining cassette paper by eight minutes. The cassette was then placed in reagent 2 containing 10 ml of 4-chloro-1-naphthol and glucose in 0·01 M phosphate buffered saline at pH 6·5. The glucose oxidase on the strip converted glucose and oxygen to gluconate and hydrogen peroxide which, in the presence of peroxidase and 4-chloro-1-naphthol, produced an insoluble blue precipitate, this formed a colour bar on the chromatography strip in five minutes. The height of the bar in mm was then read, and the level of the theophylline determined from the concentration chart appropriate for the batch of Acculevel sticks used.

HPLC was performed at the Queen Elizabeth Children's Hospital by extracting the methylxanthines together with an internal standard (3-ethylxanthine) from plasma, using a specially developed solid phase sample preparation tube and organic solvents, which were dried under oxygen free nitrogen at <40°C. The extracts were reconstituted with HPLC mobile phase, and the methylxanthines were separated on a 25 cm, 3 µ Apex 1 octadecyl-silane (ODS) column with a solvent gradient, and detected at 273 nm.[4]

Reverse phase HPLC was performed at Paddington Green Children's Hospital by the following method: isocratic chromatographic separation was carried out using an ODS 3 Partisil 10 µ column. The internal standard 8-chlorotheophylline was added to 200 µl of patient's serum, and 440 µl of acetonitrile. This was spun for 30 seconds, centrifuged for 10 minutes, and the supernatant evaporated completely under vacuum. The residue was reconstituted with 200 µl of half strength mobile phase, and after spinning a 40 μl sample was injected on to the liquid chromatography column, and detected at 273 nm

Differences between methods were analysed using a paired *t* test.

## Results

The mean difference between the theophylline concentrations obtained from the alternative assays of the individual patient samples was 0·38 mg/l. There was no significant difference between the two assay methods ($t$=1·65).

The coefficient of variation of repeated measurements for the Acculevel stick at 9 mg/l was 5·36%

## Discussion

There are various ways of measuring methylxanthines, including reverse phase HPLC,[4] gas liquid chromatography, and high pressure cation exchange chromatography, but these methods require considerable expertise. Homogenous enzyme immunoassay is simpler but still requires specific machinery which must be carefully used to obtain reliable results.[5] Theophylline stick assays are simple, reliable, and can be used by clinicians after limited training. An alternative theophylline stick assay requires the separation of plasma and a specific machine for measurement.[6]

This whole blood theophylline stick assay requires neither separation of plasma, nor expensive technology. It is particularly suitable for use outside normal working hours, casualty departments, and in small hospitals that do not have access to a therapeutic drug monitoring service. It is highly acceptable, particularly to children, as it requires only 12 μl of whole blood obtained by finger prick. As with all stick assays, care must be taken to follow the correct procedure, or inaccuracies will result.

We thank Mr J Janes of Syva (UK) for his support, Mrs Mohabir for her assistance at Paddington Green Children's Hospital, and Mr J Cromarty of the Clinical Pharmacy Unit, Northwick Park Hospital for his advice

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# Monitoring of end tidal $CO_2$ in neonatal intensive care

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SUMMARY The use of monitoring end tidal carbon dioxide pressure ($PetCO_2$) in neonatal intensive care was studied in 19 infants with respiratory disease $PetCO_2$ correlated poorly with arterial $pCO_2$, the relation being principally determined by the severity of pulmonary disease. Monitoring end tidal $CO_2$ cannot be recommended for neonates with pulmonary disease.

In modern neonatal intensive care units the continuous monitoring of arterial carbon dioxide partial pressure ($PaCO_2$) has become increasingly important. End tidal $pCO_2$ monitors, suitable for use with neonates, have recently been developed and have been proposed as alternatives to transcutaneous $pCO_2$ monitors for non-invasive monitoring of $CO_2$ content in ill premature infants. We therefore examined the accuracy and clinical usefulness of measuring the end tidal partial pressure of $CO_2$ ($PetCO_2$) in such a group of infants.

## Method

The monitor used was an Engstroem Eliza infrared capnometer. This was connected to the patient's respiratory circuit by a 15 mm endotracheal tube adapter, incorporating a standard Luer connection at right angles to the body (Respiratory Support Products), and a length of Engstroem Aridus reinforced tubing two metres long. This system permitted sampling without increasing respiratory dead space. The capnometer took samples from the airway at a constant 50 ml/min and analysed the gas continuously; it displayed $PetCO_2$ breath by breath on the monitor, together with the mean $PetCO_2$ every 30 seconds and 15 minutes, and the maximum $PetCO_2$ over a 15 minute period. The response time of the machine was 150 msec. Samples were taken from babies who were not intubated using a fine catheter inserted into the anterior nares or nasopharynx.

Infants were selected for the study if they were clinically stable and had indwelling arterial catheters. $PetCO_2$ measurements were compared with simultaneous $PaCO_2$ measurements. Infants were studied for four hours during which between one and five measurements were taken. Five infants were studied on more than one occasion at different stages of their illness.

Nineteen infants were studied, 15 while intubated (62 readings), and four while receiving oxygen or breathing air (seven readings). Their gestational ages ranged from 25 to 35 weeks (median 29 weeks), and birth weights from 744 g to 2335 g (median 1280 g). Sixteen had hyaline membrane disease of varying degrees of severity, two had transient tachypnoea of the newborn, and one had pneumonia. The severity of disease varied widely, alveolar arterial oxygen gradients (AADO) ranging from 18 to 660 mm Hg. Three of the intubated infants were having continuous positive airway pressure only, and 59 were receiving intermittent positive pressure ventilation.

Data were analysed using the Statistical Package for the Social Sciences on an IBM 3083 computer.

The alveolar-arterial oxygen gradient was estimated by the following method: $AADO=((FiO_2 \times 760)-(PaCO_2/0{\cdot}8))-PaO_2$.[1]

## Results

The capnometer recorded respiratory rate reliably whether the baby was intubated or not. It functioned well as an apnoea monitor. The nasal catheters used in non-intubated patients were poorly tolerated by the infants with respiratory distress and gave variable readings, which were affected by the position of the catheter and movement of the subject. Because of this detailed analysis has been presented only for the 62 measurements on intubated patients.

Fig. 1 is a plot of $PaCO_2$ against $PetCO_2$ showing a poor overall correlation ($r=0{\cdot}387$ $p<0{\cdot}01$). In 11 infants (32 readings) there was a useful correlation between end tidal and arterial $PCO_2$; these infants were those with mild or moderate lung disease (maximum AADO 264). This was shown by excluding all readings at an AADO of greater than 300, which considerably improved the regression ($r=0{\cdot}749$ $p<0{\cdot}0001$ $n=39$). Fig. 2 shows that the difference between $PetCO_2$ and $PaCO_2$ ($PetCO_2-PaCO_2$) correlated strongly with AADO ($r=0{\cdot}77$ $p<0{\cdot}0001$)

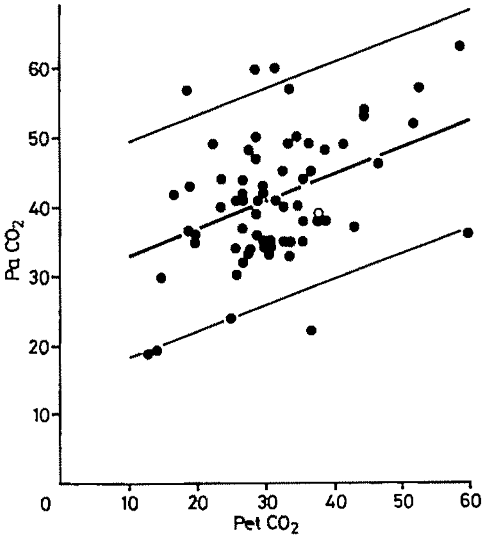

Fig 1 *Plot of $PaCO_2$ with simultaneously obtained $PetCO_2$ showing 95% confidence limits ($x=2$ values) ($r=0\ 388$ $p<0\ 01$ $n=62$)*

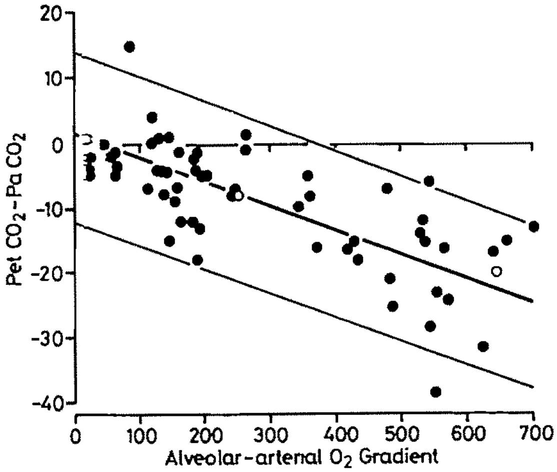

Fig. 2 *Plot of ($PetCO_2-PaCO_2$) with AADO, showing 95% confidence limits ($x=2$ values) ($r=-0{\cdot}772$ $p<0\ 0000$ $n=62$)*

Multiple regression analysis was undertaken to explore further the relative importance of the factors affecting the relation between PetCO$_2$ and PaCO$_2$. The relation between PetCO$_2$ and PaCO$_2$ could be calculated satisfactorily if PetCO$_2$ and AADO were known; in particular, the addition of respiratory rate did not significantly ($p<0{\cdot}1$) improve the accuracy of the prediction. PaCO$_2$=6·44+(0·803. PetCO$_2$)+(0·032. AADO). (r=0·725, SE=6, 12 F=32, 12 sig F<0·0001 n=60).

Infants with shorter expiratory times tended to have less accurate readings, reflected in a bigger difference between end tidal and arterial pCO$_2$ (PetCO$_2$−Pa CO$_2$). There was a poor correlation between expiratory time and this score (r=0·265 $p<0{\cdot}05$ n=62).

Infants with short expiratory times were those with more severe respiratory disease, characterised by high respiratory rate and AADO. Because of this multiple analysis of variance and covariance for the error score (PetCO$_2$−PaCO$_2$) with AADO, respiratory rate, expiratory time, and PaCO$_2$ was performed. AADO correlated strongly ($p<0{\cdot}0001$) with this score, as did PaCO$_2$ ($p<0{\cdot}0001$). Expiratory time ($p<0{\cdot}05$) and respiratory rate ($p<0{\cdot}05$) correlated weakly with this score once AADO was controlled for.

The capnometer created little extra work for nurses, requiring only the temporary disconnection of the sampling catheter during lavage and suction of the endotracheal tube. If this was neglected water was aspirated into the machine, making it temporarily useless. Calibration, taking 60 seconds, is required every three to four weeks.

## Discussion

PetCO$_2$ may be a good approximation to PaCO$_2$ but it is not identical, as it varies depending on the ventilation pattern and lung function of the subject at the time.[2–4 6] PetCO$_2$ measurements have been shown to correlate well with PaCO$_2$ in subjects without lung disease [5 6] PetCO$_2$ is most likely to equal or exceed PaCO$_2$ at high tidal volumes, high CO$_2$ outputs (as in exercise), and at low respiratory rates [3 5] PetCO$_2$ measurements considerably underestimate PaCO$_2$ in adults with lung disease or pulmonary embolism, which cause ventilation-perfusion inequality [5]

Infants with respiratory disease generally have a high respiratory rate, low tidal volume, and considerable ventilation-perfusion imbalance. It was, therefore, hardly surprising that the relation between PetCO$_2$ and PaCO$_2$ was variable and association frequently poor in this group. We have shown that AADO is the major determinant of the relation between PetCO$_2$ and PaCO$_2$, and that respiratory rate and expiratory time have a definite but less important effect

We consider that the capnometer was accurately measuring the PetCO$_2$, as in all infants the expiratory time was greater than the response time of the machine (150 msec), and in all but one was at least twice this time. PetCO$_2$ is not necessarily a good index of PaCO$_2$ in infants with severe lung disease, as in these infants alveolar ventilation is poor and may show wide regional variation, and definite ventilation-perfusion imbalance. This, coupled with the short expiratory time and high respiratory rate of these infants, may account for the large differences between these two indices.

In premature infants with respiratory distress AADO characteristically changes rapidly as the respiratory illness runs its course. The use of PetCO$_2$ is, therefore, unlikely to be helpful even as a trend monitor. Changes in the PetCO$_2$ may be due either to a change in PaCO$_2$, or to a change in the relation between PetCO$_2$ and PaCO$_2$ as the AADO changes in the course of the respiratory illness or as the ventilation pattern of the infant is changed therapeutically.

There may well be a place for PetCO$_2$ measurement in the management of premature infants with normal lung function, for example, in the detection and analysis of obstructive apnoea or during anaesthesia. For most premature infants with respiratory illness, however, this technique cannot be recommended.

We thank Mr I Grant of Gambro PLC for providing the capnometer and Mr C West of the Department of Community Health, Liverpool University, for his statistical advice Dr Watkins is supported by a research grant from the Mersey Regional Health Authority

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# Salbutamol and ipratropium in acute asthma

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SUMMARY Thirty seven children with acute asthma were given nebulised ipratropium or placebo 30 minutes after their first dose of salbutamol and eight hourly thereafter. There were no significant differences between the two groups in clinical scores, peak expiratory flow rates, length of stay in hospital, or the need for oral steroids.

Ipratropium bromide is an effective bronchodilator in children [1-3] but its place in the management of acute asthma is not clear. Storr and Lenney were unable to show any benefit when children were given a mixture of nebulised salbutamol and ipratropium compared with salbutamol alone.[4] The two drugs in sequence, however, have been reported to produce greater bronchodilatation than either used separately.[5] [6] We wanted to establish whether giving nebulised ipratropium after salbutamol conferred any therapeutic benefit over salbutamol alone.

## Patients and methods

Twenty eight boys and 12 girls, mean age 6·5 years (range 2–15), who were admitted to this hospital with acute asthma were randomly allocated to two groups in a double blind trial. All had received $\beta_2$ receptor agonists at home, but none had been given ipratropium or oral steroids. Both groups received nebulised salbutamol (2·5 mg, or 5 mg for those over 6 years old) on admission and four hourly thereafter. Thirty minutes after the first dose of salbutamol, and eight hourly thereafter, they received either nebulised placebo (3 ml physiological saline) or ipratropium (250 µg in 2 ml physiological saline). Steroids were given as usual if good relief was not obtained.

Assessments were made by one of us on admission, immediately before and 45 minutes after the first administration of the trial drug, and the next morning (12–24 hours later). Thirty one of the children were assessed by the same person (RJR). Pulse, respiratory rate, and, when possible, peak expiratory flow rate were measured. A clinical score was given, based on clinical examination, activity, and speech, the worst possible score being 25. The time taken to achieve 80% of the expected peak flow rate, or to be considered fit for discharge, was recorded.

The study was approved by the hospital ethical committee, and written consent was obtained from the parents.

The results were analysed with Student's *t* test. We calculated that a difference of more than 3 in clinical score, or 15% of the expected peak expiratory flow rate, between the two groups would be significant ($p<0·05$).

## Results

Two children failed to comply with the nebuliser treatment and one required intravenous treatment immediately after being given salbutamol, leaving 18 in the control group and 19 in the treatment group. The groups were closely matched for age and sex distribution, mean clinical scores, and peak flow rates on admission. Fourteen in the control group and eight in the treatment group were taking prophylactic drugs. Seven in the control group and 10 in the treatment group were using a nebuliser at home.

There was a significant response to salbutamol in both groups (Student's *t* test, $p<0·001$), but there were no significant differences between the two groups in mean clinical score or peak expiratory flow rate after the first dose of the trial drug, or the next morning (Tables 1 and 2).

Table 1 *Mean (SEM) clinical scores*

| | *Control group (n=18)* | *Treatment group (n=19)* |
|---|---|---|
| On admission | 12·2 (0·8) | 12·7 (0·8) |
| After salbutamol | 9·1 (0·8) | 8·6 (0·9) |
| After trial drug | 7·6 (0·7) | 6·6 (0·7) |
| Next morning | 3·9 (0·3) | 4·6 (0·7) |

Table 2 *Mean (SEM) peak expiratory flow rates as percentages of expected values*

| | *Control group (n=12)* | *Treatment group (n=8)* |
|---|---|---|
| On admission | 36·9 (2·5) | 32·2 (2·6) |
| After salbutamol | 51·0 (4·4) | 55·4 (7·0) |
| After trial drug | 56·6 (4·8) | 57·4 (9·0) |
| Next morning | 72·0 (4·6) | 70·4 (6·5) |

The mean (SEM) length of stay in hospital was 23·9 (3·3) hours in the control group and 24·5 (2·5) hours in the treatment group. Fourteen (78%) of those in the control group and 14 (74%) of those in the treatment group required oral steroids. Only one child (in the treatment group) required intravenous aminophylline, 15 hours after his admission and six hours after his second dose of ipratropium

## Discussion

Sixteen out of 37 children scored 13 or more on admission and 17 out of 19 children had a peak expiratory flow rate below 50% of the expected value Nevertheless, we were unable to show significant benefit from the sequential use of nebulised ipratropium in addition to salbutamol. Therefore, although it may be valuable in individual children, the routine use of ipratropium in acute asthma cannot be recommended

We thank Dr E J Hiller and Dr D A Curnock for allowing us to study their patients, the pharmacy department at the City Hospital for preparing the solutions, and the nursing staff of Papplewick Ward

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# Prader-Willi syndrome in siblings, due to unbalanced translocation between chromosomes 15 and 22

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SUMMARY In a family in which the father carried a balanced translocation between chromosomes 15 and 22 two of his children had Prader–Willi syndrome and an unbalanced chromosome complement, having lost the proximal bands from the long arm of chromosome 15. His four other surviving children were normal but carried a balanced translocation

## Case report

The proband, who was 5 years old at the time of writing, was admitted to the special care baby unit when 3 days old with extreme hypotonia and feeding difficulties. He had been born to a consanguineous Asian couple and was the product of an uneventful pregnancy that had progressed to term; he had been delivered vaginally. Birth weight was 2020 g, and he appeared otherwise normal apart from bilaterally undescended testes and a small scrotum Tube feeding was necessary for two months. His development was delayed both physically and mentally: he walked at the age of 3½ and attended a special school for the educationally subnormal

His next younger sibling had identical problems and was managed in the special care baby unit from the age of 5 days. He also was tube fed for two months. At over 1 year old he had a developmental age of 9 months and hypogonadism.

The family details are shown as a pedigree in Figure 1

## Cytogenetics

The proband was found to have a deletion of chromosome 15 during a study of children diagnosed as having Prader-Willi syndrome.[1] In this study high resolution G banding and Distamycin/DAPI fluorescence were used.[2] This technique is valuable for defining the intense fluorescence that is characteristic of the short arms of chromosome 15.

There was no intense fluorescence on the short

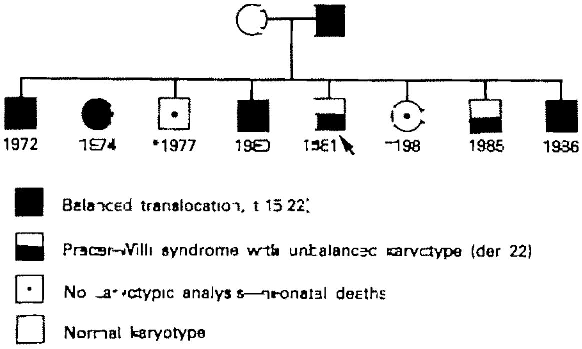
1972
1974
*1977
1980
1981
†198
1985
1986
Balanced translocation, t 15 22;
Prader-Willi syndrome with unbalanced karyotype (der 22)
No karyotypic analysis—neonatal deaths
Normal karyotype

Fig. 1 *Pedigree showing chromosome results. *Death at one week, cause unknown †Stillbirth due to hydrocephalus.*

arms of the deleted chromosome 15, and it was thought, therefore, that this might be attributable to a translocation between two acrocentric chromosomes. Chromosome studies of blood from the parents confirmed that the father carried a balanced translocation, t(15;22) (q13;q112) (Figure 2a). The two siblings with the syndrome were effectively monosomic for the short arm and proximal long arm of chromosome 15 and trisomic for the short arm and proximal region of chromosome 22 (Figure 2b).

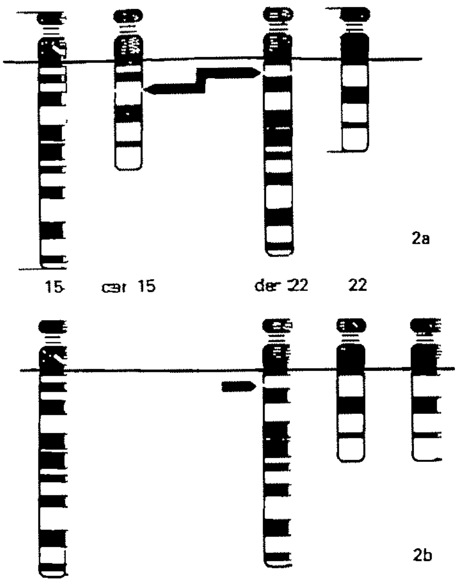

Fig. 2 *(a) Partial idiogram of balanced translocation in the father, 46XY, t(15,22) (q13,q12), (b) idiogram of unbalanced chromosomes of affected children, 45XY, −15, +der (22). They are monosomic for short arm and proximal long arm of chromosome 15 and trisomic for short arm and centromeric region of chromosome 22*

The surviving siblings carried the balanced translocation. Studies were not done on the two infants who died in the perinatal period. This was unfortunate as the segregation ratio here was unusual with all six karyotyped children carrying the paternal translocation in either a balanced or an unbalanced form.

## Discussion

Prader-Willi syndrome in siblings is rare.[3] After Hawkey and Smithies described a child with this syndrome and a translocation involving chromosome 15[4] many abnormalities of chromosome 15 with Prader-Willi syndrome have been reported; a small interstitial deletion of 15q112 is the most consistent finding. Butler *et al* reviewed the clinical and cytogenetic findings.[5]

Only about half of all cases can be diagnosed from chromosomal analyses. The finding of normal chromosomes does not rule out the possibility of Prader-Willi syndrome. In our case a previously unreported chromosomal abnormality was present and hence helped the diagnosis in both the affected and the carrier siblings.

Early diagnosis and counselling helped the parents understand the need for dietary control in the affected children. The proband did not put on a large amount of weight and was just on the third weight percentile for his age. The parents' religious beliefs precluded preventing the birth of further affected children, but, clearly, genetic counselling of the siblings carrying the translocation will be important.

We thank Dr K C Cheetham, consultant paediatrician, Wycombe General Hospital, who kindly permitted use of his notes and Dr J A Jonasson, department of cytogenetics, Oxford, for the cytogenetic information on the younger children, thanks are also due to Dr B Laurance, who gave constructive criticism, and Claudine Fear for her cytogenetic help

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# Green or blue light phototherapy for neonates with hyperbilirubinaemia

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SUMMARY A total of 262 neonates were treated with green (350–650 nm) or blue (300–600 nm) light phototherapy for a similar length of time. There was no significant difference in the rate of bilirubin photodegradation between the groups.

The possibility of using equally effective but safer spectral areas than the conventional 420–490 nm (blue part of the spectrum), in the treatment of neonatal jaundice is currently being investigated. It has been shown that green light is more effective than white in reducing serum bilirubin concentrations in preterm neonates.[1]

The purpose of the present study was to evaluate the efficacy of green versus blue light in reducing serum bilirubin in term and preterm neonates with hyperbilirubinaemia.

## Patients and methods

Standard 20 watt sylvania F20T12G (green) or F20T12B (blue) fluorescent tubes were mounted on to conventional phototherapy units with five tubes each to provide the light source. The emission spectra were estimated with a Baush-Lomb 250 monochromator. The radiance of the lamps was measured from 50 cm away with a research IL 700 radiometer. The integrated emission energy was 0·326 milliwatt for the green light and 0·261 milliwatt for the blue light. A total of 262 neonates with jaundice of unknown aetiology were included, overt haemolysis having been excluded. They were separated into two groups according to their gestational age; 200 were born at term (≥37 weeks) and 62 before term (<37 weeks). They were then randomly allocated into two subgroups to receive either green or blue phototherapy (Table 1).

Table 1 *Clinical and laboratory characteristics of the neonates*

| *Characteristics* | *Full term neonates* | | *Preterm neonates* | |
|---|---|---|---|---|
| | *Green light (n=100)* | *Blue light (n=100)* | *Green light (n=31)* | *Blue light (n=31)* |
| Gestational age (weeks) | 38·88 (0·131) | 38·99 (0·127) | 34·70 (0·374) | 34·58 (0·340) |
| Birth weight (g) | 3391 (43) | 3397 (44) | 2418 (90) | 2304 (80) |
| ½ body surface ($cm^2$) | 1063 (12·7) | 1055 (9·2) | 838 (25·5) | 832 (20·5) |
| Age at the start of phototherapy (hours) | 105·00 (2·62) | 98·53 (3·09) | 87·45 (4·93) | 83·73 (5·52) |
| Duration of phototherapy (hours) | 42·68 (2·74) | 49·88 (3·02) | 53·26 (5·52) | 53·29 (5·90) |

Values are given as mean (SD), none of the differences were significant at the 5% level

Table 2 *Serum bilirubin measurements*

| *Serum bilirubin measurements* | *Full term neonates* | | *Preterm neonates* | |
|---|---|---|---|---|
| | *Green light (n=100)* | *Blue light (n=100)* | *Green light (n=31)* | *Blue light (n=31)* |
| Rate of rise before phototherapy (μmol/l/h) | 3.27 (0.22) | 3.32 (0.19) | 3.32 (0.63) | 3.16 (0.46) |
| At start of phototherapy (μmol/l) | 288 (2.5) | 284 (3.2) | 251 (12.7) | 227 (9.3) |
| Rate of fall during phototherapy (μmol/l/h) | 3.27 (0.22) | 2.86 (0.17) | 2.91 (0.38) | 2.50 (0.39) |
| Rate of fall during phototherapy (μmol/l/h/cm$^2$/mW×10$^{-5}$) | 935 (56) | 1036 (61) | 1088 (148) | 1136 (196) |
| At the end of phototherapy (μmol/l) | 246 (3.23) | 245 (3.08) | 214 (9.54) | 192 (8.41) |
| Rate of rise (postphototherapy) rebound—μmol/l/h) | 0.24 (0.07) | 0.31 (0.10) | 0.60 (0.24) | 0.40 (0.12) |

Values are given as mean (SD), none of the differences were significant at the 5% level

Informed consent was obtained from the parents of those neonates who were to receive green phototherapy. The serum bilirubin concentration was measured every six hours before and during phototherapy and for 48 hours after stopping the treatment. Measurements were made on capillary samples using a bilirubinometer (American Optical Corporation). Phototherapy was stopped when two consecutive reductions in bilirubin concentration had been obtained. The quantum efficiency of bilirubin photodegradation (mg/hour/cm$^2$/milliwatt) was estimated, taking into account the differential emission energy of green and blue fluorescent lamps. The results were analysed using Student's two tailed *t* test.

## Results

There were no significant differences in the clinical characteristics between the two groups (Table 1).

The results are presented in Table 2. There were no significant differences between the phototherapy groups in the rate of fall of serum bilirubin concentrations, the duration of phototherapy, and the serum bilirubin concentration at the end of treatment. There was no significant difference in the rebound rise in serum bilirubin concentrations after phototherapy between the two groups.

## Discussion

The wavelengths with the greatest photodegrading effect on bilirubin are between 420 and 450 nm. In cultures of procaryotic and eucaryotic mammalian cells exposure to this range of wavelengths results in the highest number of DNA breaks, mutation, and sister chromatid exchanges.[2] Sister chromatid exchanges were also found in lymphocytes in peripheral blood of jaundiced neonates receiving blue light phototherapy.[3] The fact that these photobiological changes are reduced after exposure to wavelengths greater than 500 nm led to the evaluation of phototherapy using other parts of the spectrum. Green light is more effective than white, and equally as effective as the special blue light in reducing serum bilirubin in preterm neonates.[1 4] The present study included more jaundiced full and preterm neonates than previous studies and it is the first to our knowledge to estimate and compare the quantum efficiency of the green and blue light.

It has been suggested that bilirubin photodegradation with green light is mainly achieved through formation of lumirubin,[5] but the binding of fatty acids to albumin has a definite effect on the absorption spectrum of bilirubin, shifting it towards longer wavelengths.[6] In addition we have shown (unpublished data) in in vitro studies using aqueous solutions of bilirubin bound to albumin exposed to green or blue light, that the higher the concentration of bilirubin the larger the overlapping between the absorption spectrum of bilirubin and the emission spectrum of the green fluorescent lamps. Clinically green light may result in greater peripheral vasodilation and increased skin perfusion (because of its greater thermal energy) than the blue light, resulting in a greater part of the total bilirubin load being exposed to its effect.

We conclude that green light could be used for the treatment of neonatal jaundice as it is as effective as blue light, and is possibly less potentially harmful to both babies and nurses.[7] Although green light is clinically effective, we recommend that studies specifically designed to elucidate its mode of action on bilirubin and fully evaluate its biological effect should be carried out.

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# Indicators of malnutrition in leukaemic children

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SUMMARY In 24 children with acute leukaemia a low serum albumin concentration (31 g/l or less) and a median weight:height ratio of less than 0·95 on admission were indicators of severe weight loss.

Malnutrition is a problem in children with cancer. Severe weight loss and malnutrition as causes of morbidity and mortality were quantified by Cahill, who established that the loss of 30% of lean body weight was incompatible with life.[1] There are many causes of cancer cachexia. Patients with leukaemia are often affected, and both acute weight loss at presentation and persistent malnutrition are commonplace. Acute weight loss may be due to anorexia, malabsorption, excessive energy loss, ineffective metabolic activity, chemotherapy, and psychosocial factors. Whatever the causes, children who are malnourished when treatment is started have a worse prognosis than their counterparts who are well nourished.[2-4] This may be due to factors inherent in the disease, or may be the result of ineffective treatment being given while waiting for their nutritional state to improve. In this retrospective study we tried to find out the risk factors that would help predict which children would benefit from supplementary nutrition.

## Patients and methods

Twenty four new patients with acute leukaemia aged between 1·2 and 14·8 years were studied They were retrospectively divided into two groups of 12 children. Group I comprised four boys and eight girls who needed supplementary nutrition. In Group II were 10 boys and two girls who did not need supplementary nutrition. On admission all children had a standard physical examination including measurement of height and weight. All children were treated according to the protocol of the Medical Research Council Childhood Leukaemia Trial. During their stay in hospital they were weighed regularly. The parents were advised by the dietician on what to give their children to eat. The children were offered food from the hospital kitchen, but parents provided alternative foods if the children requested items that were not available. During the course of treatment, if a child lost more than 10% of the admission weight he or she was given either nasogastric Fortisan 2·09 MJ (500 kcal)/500 ml by nasogastric tube or total parenteral nutrition. Total parenteral nutrition was given to those who were too ill to tolerate nasogastric feeds or who were unlikely to benefit from enteral feeding because of diarrhoea and malabsorption.

On admission (in addition to the other recommended haematological and biochemical tests) serum albumin concentration was estimated, and this was monitored weekly thereafter. The data obtained were used to determine which group of children required supplementary nutrition during the course of their treatment and to find out if there were any features apparent on admission that would predict which children would need nutritional support. The median weight:height ratio was calculated as the ratio of weight over height divided by weight over height at the 50th centile.[5] The ratio may be expressed as a percentage. The paired $t$ test was used to analyse the results.

## Results

The mean value for median weight:height ratio for children in group I was significantly lower than that for children in group II. The mean (SD) values were 0·95 (0·11) and 1·0 (0·1) or, expressed as a percentage, 95% (11%) and 100% (10%), respectively ($p<0\cdot01$) (Fig. 1). The mean value for median weight:height ratio was still significantly lower by the fourth week in hospital. The mean serum albumin concentration of children in group I was significantly lower than that of children in group II on admission, being 31·5 (2·5) g/l in group I and 35·6 (2·5) g/l in group II ($p<0\cdot01$), but not different at four weeks (Fig 2).

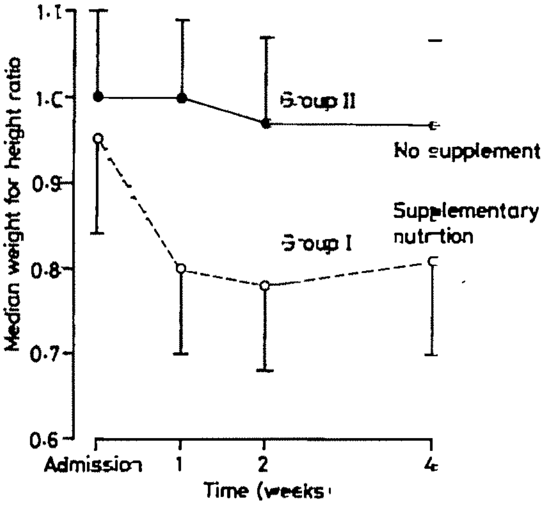

Fig 1 *Change in median weight:height ratio*

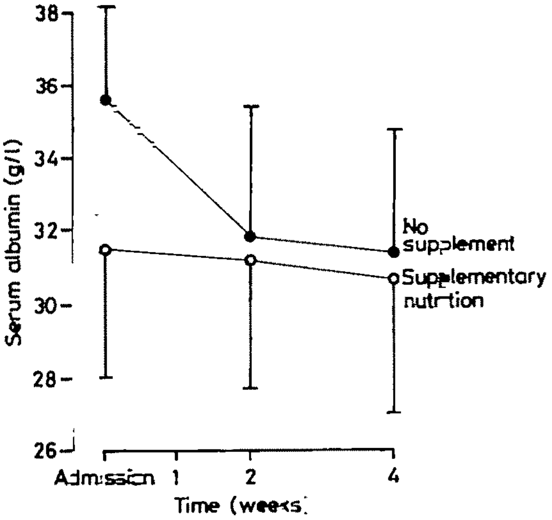

Fig 2 *Fall in serum albumin concentrations*

## Discussion

Although malnutrition is known in children with cancer, prospective assessment of nutritional state has not often been studied. For many children the start of chemotherapy tips the balance from adequate nourishment to malnourishment. Standard measurements of nutrition state need to be used regularly in these children, who at the time of admission may be on the borderline of adequate nutrition. We have found that the median weight. height ratio and the serum albumin concentration may be useful measurements in newly diagnosed children with leukaemia to indicate which children will require supplementary nutrition. Rickard *et al*[6] published criteria for the nutritional staging of children with neoplastic disease. They suggested that a weight loss equal to or greater than 5% was bad. They also reported that if weight was below the fifth percentile when the height was greater than the fifth percentile, then the child was at risk of malnutrition. The third criteria was a serum albumin concentration of less than 32 g/l.

Actual weight at onset of symptoms is difficult to ascertain; we find the other two criteria more practical In our study group those with a median weight:height ratio of less than 0·95, and a serum albumin concentration of less than 31 g/l, were considered malnourished and needed supplementary nutrition The median weight for height showed a dramatic fall and could be used for continuing assessment, but serum albumin concentration did not show the same reduction.

We thank Mrs N Woodward for help in preparation of the manuscript. MSK is supported by the Leukaemia Research Fund

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# Stress fractures: a diagnostic problem

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SUMMARY Three cases of stress fracture, in which diagnosis was aided by sequential radiographs and radionuclide scanning are presented; and a procedure for their management, which attempts to eliminate the need for invasive investigations, is suggested

Stress fractures in children may present diagnostic dilemmas, as they may have clinical and pathological features in common with infectious or malignant conditions.[1-3] Although stress fractures have been described previously, the associated problems have received scant attention in published reports

## Case reports

**Case 1.** A previously healthy 9 year old girl presented at the day care unit with a three week history of pain in the right shin and a mild limp. The pain was constant during the day, but disappeared at night. There was no history of trauma nor was there any evidence of an underlying bony or metabolic disorder, febrile illness, or weight loss. Physical examination showed a mild swelling and local tenderness in the proximal and medial aspects of the right tibia. Blood count, erythrocyte sedimentation rate, and serum calcium and phosphorus concentrations and alkaline phosphatase activity were normal.

Radiographs of the right tibia at the time of initial evaluation showed a thick lamellar periosteal reaction over the proximal and medial aspect of the tibia; no fracture line was evident, and $^{99m}$Tc radionuclide scintigraphy showed increased uptake across the proximal part of the tibia (Figure 1).

A computed tomography scan showed a nonspecific region of slightly increased medullar density. A bone biopsy was considered and postponed, and during three weeks observation the symptoms progressively resolved. Serial radiographs showed thickening of the periosteal reaction and the appearance of a horizontal fracture line (Figure 2). A second bone scan, carried out after three weeks showed decreased uptake when compared with the previous one and confirmed the diagnosis of stress fracture of the right upper tibia. Only then did we learn that the patient was an amateur ballet dancer

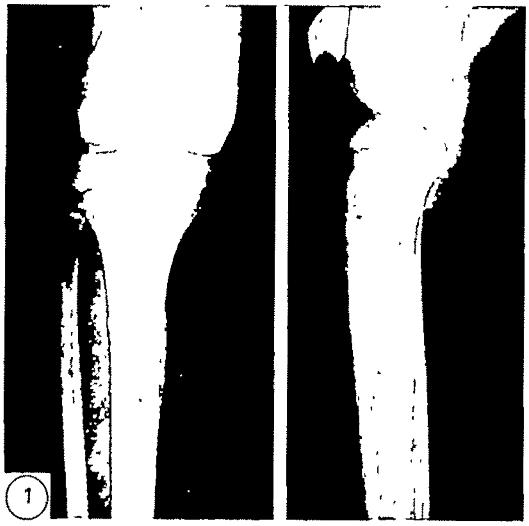

Fig 1 *Thick lamellar periosteal reaction over proximal posterior and medial aspect of the shaft of right tibia*

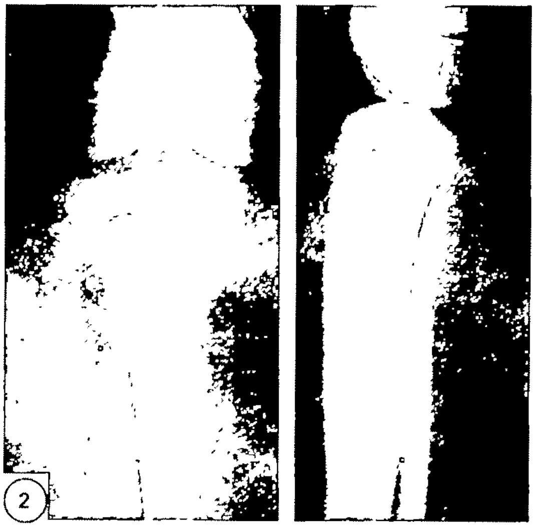

Fig 2 *Three weeks later thickening of periosteal reaction and appearance of horizontal fracture line.*

**Case 2.** A previously healthy 10 year old boy presented with a two week history of pain in the right tibia and a mild limp. The pain worsened during exercise and lessened at rest. There was no history of trauma. Physical examination yielded normal results, except for some swelling and tenderness at the medial aspect of the right tibia. All laboratory investigations gave normal results. Radiographs of the right tibia at the time of initial evaluation showed a thick periosteal reaction over the medial aspect of the upper shaft of the tibia with a blurred zone of the compact bone at the medial and posterior aspect. Computed tomography did not help, but radionuclide scintigraphy showed increased activity. Although the clinical and roentgenographic findings suggested stress fracture with subperiosteal haematoma, the possibility of a bone tumour could not be excluded. Complete rest was ordered. During the subsequent six weeks of follow up his symptoms progressively resolved. The *x*-ray findings did not change but a second bone scan clearly showed decreased activity compared with that of the first. Subsequent radiographs and bone scans performed three and eight months after admission yielded normal results.

**Case 3.** A 13 year old girl was admitted because of pain just below the left knee, which had lasted for about 10 days. There was no history of trauma. Physical examination showed slight tenderness and a mild swelling of the proximal medial aspect of her left tibia. Laboratory investigations showed no abnormality. Radiographs of the affected tibia showed thickening of an area of compact bone over the proximal and medial aspect of the metaphysis. A radionuclide scan showed increased activity across the affected area of the tibia, and a stress fracture was suspected. Her symptoms subsequently resolved; there was improvement on radiography and decreased uptake over the affected area on bone scan. Stress fracture was confirmed.

## Discussion

These three cases represent different presentations of stress fractures in children. Such injuries are uncommon in children, probably because of the increased flexibility of immature bones.[3] Devas[1] has shown that the most common site of a stress fracture in a child is the upper third of the tibia, and our case studies confirmed this. In adults the clinical history is the most important feature in diagnosis. The classic history is limb pain that recurs with a particular activity and is relieved by rest.[4] In children, however, the difficulty in obtaining a detailed history greatly limits the physician in this diagnosis (case 1).

The differential diagnoses include osteoid osteoma, infection, osteosarcoma, and Ewing's sarcoma.[1 3] Laboratory estimations—for example, blood count and erythrocyte sedimentation rate—may help to rule out osteomyelitis. The possibility of a tumour, however, is of great concern. In certain cases the distinction between these two conditions may be difficult because the suggestive history of stress fracture is often lacking in children and the clinical and diagnostic findings are usually not helpful. Furthermore, even bone biopsies are not always reliable for definitive diagnosis, because a healing stress fracture may histologically resemble a bone sarcoma or a Ewing's tumour.[1 3] Misdiagnosis has been emphasised by Engh,[2] who described nine children with stress fractures who had initial diagnoses of osteoid osteoma, low grade osteitis, and osteosarcoma.

Resolution of symptoms, typical serial *x* ray changes appearing two to three weeks after the onset of symptoms,[1 4] and an initial positive radionuclide bone scan that reverts to normal within four to six weeks,[5 6] may help to establish the diagnosis.

We therefore agree with Devas[1] and Engh,[2] who maintain that if there is any possibility that a bone lesion may represent a healing stress fracture biopsy should be avoided unless there is clear evidence that the lesion has not changed radiographically for several weeks. The dilemma of whether to biopsy the lesions was raised in all our cases. In cases of bone lesions with no expansion of the pathological process to the soft tissues, where a bone tumour is not highly suspected and all laboratory results are within normal limits, a policy of observation for a short period should therefore be adopted. In the interim complete rest should be ordered and close follow up started. Such management will avoid unnecessary biopsies.

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# Single dose and pulsatile treatment with human growth hormone in growth hormone deficiency

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SUMMARY The growth and growth hormone profiles in four children receiving three different regimens of treatment with human growth hormone (hGH) were compared. There was no significant difference in the rate of growth between the regimens; the rate of growth fell dramatically after treatment. Pulsatile administration of hGH was no better than conventional treatment

In the United Kingdom the conventional treatment of growth hormone deficiency has been 4 IU pituitary human growth hormone (hGH) given intramuscularly three times a week.[1] In an attempt to reproduce the normal physiological pattern of secretion of growth hormone, and thus achieve a greater growth response, the same total weekly dose has been given in daily subcutaneous injections.[2–4] Studies in animals, in which the hormone was given intravenously, indicated that frequent doses are more effective than occasional ones [5] There are no data about pulsatile administration of hGH subcutaneously either in animals or in man; we therefore studied the effect of pulsatile administration on the rate of growth in a small group of children deficient in growth hormone.

## Patients and methods

Four prepubertal children deficient in growth hormone (one boy and three girls with a mean age of 7·6 years, range 6·1–11·4 years) were studied. Three had already received the standard regimen (4 IU intramuscularly) and one was a new patient. The Table summarises their clinical details. The study was approved by the Middlesex Hospital ethics committee, and informed consent was obtained from the patients' parents. Recruitment to the study stopped in May 1985, when hGH was withdrawn from the market.

A single blind study was performed. Each child received, in random order, one bolus of 2 IU hGH or three boluses of 0·6 IU hGH each night for six nights through a 27 gauge infusion needle inserted subcutaneously into the anterior abdominal wall, a mini infusion pump (engineering department of the National Institute for Medical Research, Mill Hill) was used. An interval of 3·3 hours separated each dose in the multiple pulse regimen The hGH was prepared weekly and kept in a refrigerator After six months each child changed to the other regimen.

Growth hormone profiles were constructed for each child during the three regimens, blood samples being taken at 20 minute intervals, for 12–24 hours, through an indwelling heparinised venous cannula Serum growth hormone concentrations were measured by immunoradiometric assay.

Auxological data were collected at three monthly intervals by standard techniques.[6] The rate of growth is reported as raw data (centimetres per year) and the standard deviation score, defined as $(X-\bar{X})/S$, where X is the rate of growth, $\bar{X}$ the mean rate of growth, and S the standard deviation for age and sex.

Table *Clinical and auxological data*

| | *Case 1* | *Case 2* | *Case 3* | *Case 4* |
|---|---|---|---|---|
| Age at start of study (years) | 6·1 | 6·6 | 6·4 | 11·4 |
| Diagnosis | GHD, TSHD | GHD | GHD | GHD |
| Years of treatment with hGH | 3·5 | 4·0 | 3·5 | None |
| Rate of growth[*] | | | | |
| Before treatment | 6·4 (−1·8) | 5·9 (−1·8) | 4·0 (−2·9) | 4·1 (−2·0) |
| During treatment | | | | |
| 4 IU hGH intramuscularly[†] | 5·6 (−0·7) | 6·2 (+0·9) | 3·9 (−2·3) | Not applicable |
| 2 IU hGH subcutaneously | 5·6 (−0·6) | 6·1 (+0·5) | 6·0 (+0·3) | 9·9 (+3·8) |
| 0·6×3 hGH subcutaneously | 5·4 (+0·3) | 3·2 (−2·9) | 6·2 (+0·2) | 9·0 (+3·0) |
| After treatment | 0·6 (−5·7) | 3·8 (−2·0) | 1·4 (−5·1) | 3·3 (−2·5) |

GHD=Growth hormone deficiency TSHD=Thyrotrophin stimulating hormone deficiency

[*] Expressed as cm/year with standard deviation score in parentheses

[†] Steady state growth rate

## Results

The Table summarises the results. When given the conventional regimen the new patient showed 'catch up' growth, which was maintained during both subcutaneous regimens. The rate of growth in the three children who had previously been treated was maintained or improved, although during the 0·6 IU regimen in case 2 the rate of growth fell because of non-compliance.

The rate of growth and standard deviation score of each child fell dramatically after treatment stopped, the score falling from the mean pretreatment value of −2·1 (confidence interval −1·8 to −2·9) to −3·8 (−2·5 to 5·7) after treatment.

The growth hormone profiles from one patient are shown in the Figure and compared with the profile of a 6 year old boy growing at a rate yielding a standard deviation score of −0·6. Actual time is not shown as the injection times were not synchronous, spanning 2000–2100. The peak concentrations of growth hormone and areas under the curves were greatest during the highest dose regimen, but the mean time to the peak concentration was similar after 4 IU hGH given intramuscularly, 2 IU hGH given subcutaneously, and the first pulse of 0·6 IU given subcutaneously (3·6, 3·9, and 2·8 hours, respectively); similar times were seen after the subsequent pulses. Peaks of growth hormone concentration were seen during the three dose regimen in all cases. The peak concentration and area under the curve were less than in the two other regimens, but the profile resembles the normal secretory pattern of growth hormone more closely than the profiles seen during the other regimens.

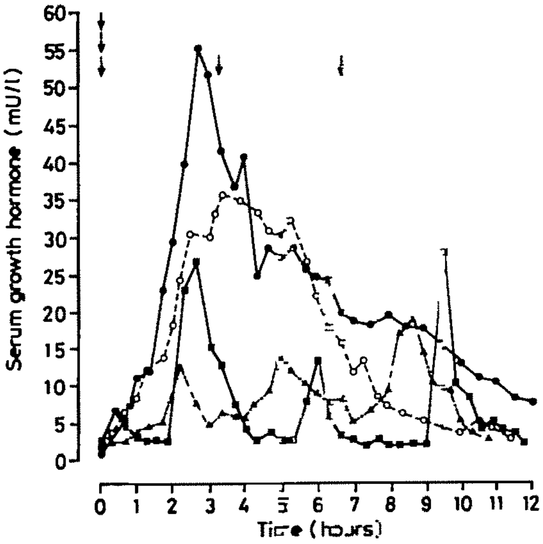

Figure *Serum growth hormone profiles in a normal prepubertal boy* ■——■, *and after* ↓ *4 IU human growth hormone administered intramuscularly* ●——●, ↓ *after 2 IU human growth hormone administered subcutaneously* ○——○; *and after* ↓ *0·6 IU human growth hormone administered subcutaneously* ▲- - -▲ *in children deficient in growth hormone*

## Discussion

In the United Kingdom a Medical Research Council working party concluded that an acceptable cost-benefit ratio in the treatment of children deficient in growth hormone was achieved when a total weekly dose of 12 IU hGH was given intramuscularly in three equal doses [1] Albertsson-Wikland *et al* and Kastrup *et al* reported improved growth when hGH was given daily but in the same weekly dose to children previously established on the conventional regimen [2 3] More frequent injections in animals have produced a greater growth response.[5] In this small study we compared the effects on growth and serum growth hormone concentrations during treatment with 4 IU hGH intramuscularly three nights a week, 2 IU hGH subcutaneously six nights a week, and 0·6 IU hGH subcutaneously six nights a week We showed similar growth responses in all treatment groups despite greater serum concentrations of growth hormone during the two high dose regimens compared with the multiple pulse regimen A longer study with larger numbers of patients to confirm or refute our results was not possible because hGH was withdrawn from the market.

We were unable to show any resemblance between the growth hormone profile after 2 IU hGH and the normal secretory profile, as reported by Christiansen *et al*,[4] The multiple pulse regimen came closer to replicating the normal profile in childhood. To mimic normality higher doses of growth hormone are required, and it would probably have to be given intravenously as in the animal experiments [5]

The growth rates fell noticeably after treatment. A similar phenomenon was observed in a matched group (age, sex, and pubertal development) of 15 children deficient in growth hormone whose pretreatment rate of growth standard deviation score of −2·1 (SD 1·0) fell to −3·2 (SD 1·5) during the period after growth hormone was withdrawn from the market ($p<0·01$) (C G D Brook *et al.* Paper presented at meeting of European Society of Paediatric Endocrinology, Zurich, 1986) Tanner *et al* described 'regulatory' deceleration after withdrawal of treatment with hGH, with the effect waning by six months.[7] We confirmed these findings but found that the phenomenon was still present nine to 12 months after the end of treatment

The optimal treatment regimen has yet to be established, but this may now be possible as synthetic growth hormone becomes more widely available

We thank the locally organised clinical research committee of the North East Thames Regional Health Authority and Children Nationwide Medical Research Fund for financial support

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# Diagnosis of rotavirus gastroenteritis by smell

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SUMMARY Clinical features cannot differentiate rotavirus gastroenteritis from other types of diarrhoea. Sixty eight stool specimens were examined by nurses on an infant gastroenteritis ward. Of these, 69% were correctly classified by smell alone. The results are significant ($p=0\cdot009$) and support the suggestion that rotavirus stools have a characteristic smell

The appearance and smell of stools have always interested physicians,[1] and the smell of the stool has provided an important clue in establishing the original link between enteropathogenic *Escherichia coli* and neonatal gastroenteritis.[2] The present study was undertaken because it was noticed that the nurses on a paediatric infectious disease ward usually diagnosed rotavirus gastroenteritis correctly before the results of culture were available They considered the appearance and smell of the stools to be of diagnostic value. Our aim was to test the hypotheses that rotavirus gastroenteritis could be diagnosed by either the smell of the stool alone, or a combination of smell and appearance.

## Patients and methods

Overnight stools were collected from 23 babies with diarrhoea, aged 0–18 months (mean 4·8 months), and coded by night staff. Table 1 shows the causes of the diarrhoea. The stools were randomised and examined by day staff at 9.00 am the next morning.

Each stool was examined in two ways The first way by smell alone, the specimen pot being wrapped in a paper towel, and the nurse keeping her eyes closed. She was asked to classify it as rotavirus or not rotavirus; 'don't know' was not allowed. For the second examination the paper towel was removed and she was asked to inspect the stool and given the opportunity to change her opinion. Seven nurses made 68 examinations of 33 stool specimens over three months.

The ages of the children, the feeds given, and the ages of the stools were comparable.

Table 1 *Diagnoses in 23 babies studied*

| *Diagnosis* | *No of babies* |
|---|---|
| Positive for rotavirus | 10 |
| Rotavirus only | 8 |
| Rotavirus and adenovirus | 1 |
| Rotavirus and enteropathogenic *E coli* | 1 |
| Not positive for rotavirus | 13 |
| Adenovirus | 2 |
| *Campylobacter* | 1 |
| Respiratory infections | 4 |
| Cystic fibrosis | 2 |
| No organism isolated | 4 |

Table 2 *Correlation of diagnosis by smell of stool and by culture*

| *Diagnosis from culture* | *Nurse's diagnosis by smell of stool* | | *Total* |
|---|---|---|---|
| | *Nurse positive for rotavirus (%)* | *Nurse negative for rotavirus (%)* | |
| Positive for rotavirus | 10 (38) | 16 (62 | 26 |
| Negative for rotavirus | 5 (12) | 37 (88 | 42 |
| Total | 15 (22) | 53 (78 | 68 |

## Results

Table 2 shows the results of examination of stools by smell alone. Sixty nine per cent of stools were classified correctly. The sensitivity was 38% ($\chi^2$ using Fisher's exact test; p=0·01) When the variation between nurses was taken into account the significance was unchanged (Cochrane's test; p=0·008). The information about stool appearance did not materially affect the results.

## Discussion

Experienced nurses classified most of the stools by smell alone; it seems likely, therefore, that stools infected by rotavirus have a distinctive smell. As stools infected with enteropathogenic *E coli* also have a characteristic smell, it may be that other organisms causing diarrhoea may also be identified by smell.

None of the clinical features of rotavirus diarrhoea distinguishes it clearly from diarrhoea caused by other organisms, though studies of inpatients have suggested that fever, frequent vomiting, isotonic dehydration, and lack of white cells in the stools are more commonly associated with diarrhoea caused by rotavirus.[3] [4] The smell of the stool could, therefore, be a useful aid in diagnosis.

Only 38% of the stools containing rotavirus were correctly identified, so the sensitivity of smell alone as a diagnostic test is low. These results might be improved if the nurses were told the results of culture at the time they made their diagnosis, and allowing them to change their minds in cases of uncertainty.

It is not clear what causes the distinctive smell; rotavirus damages the mucosa of the small intestine directly, not by producing a toxin. Its effect on stool composition, therefore, is probably indirect disruption of normal gut function, or a change in the normal gut flora

Damage to the brush border reduces disaccharide concentration both in man and animals, and endopeptidases are probably also affected in this way.[5] Disaccharides and peptides may, therefore, be present in the stools in increased concentrations. Derivatives, such as lactic acid, are volatile and pungent, and could affect the smell of the stools.

Any change in the composition of colonic fluid will unbalance the normal flora which carry out many metabolic processes. Such change could affect the relative concentrations of pungent products, including short chain fatty acids and indoles, thereby altering the smell.

Disturbances in the fatty acid and bile acid concentrations in stools have been shown in patients with chronic diarrhoea by chromatography, and this might also be a useful technique for diagnosing acute gastroenteritis in children.[6]

We conclude that the smell of the stools of infants with acute gastroenteritis may help to diagnose rotavirus and possibly, other infections.

We thank Sisters Treadwell and Ostrowska and the nurses on ward 31 at East Birmingham Hospital without whom we could not have carried out this study

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# Hypogammaglobulinaemia and negative anti-HIV antibodies in AIDS

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SUMMARY Repeated bacterial infections are frequent in children with AIDS owing to the B cell abnormalities produced by HIV infection. We report on two infants who presented with hypogammaglobulinaemia and with no HIV antibodies, but with epidemiological, immunological, and clinical features of AIDS.

Acquired immune deficiency syndrome (AIDS) in childhood, particularly in infants, is different from the adult disease. Epidemiological studies indicate that 18% of affected children have been transfused with contaminated blood products, 73% of them have parents who are at risk, and in the rest the source of the virus is unknown. The most common clinical features are chronic pneumonitis, enlarged liver or spleen with or without lymphadenopathy, failure to thrive, and recurrent infections

It is difficult to distinguish infantile AIDS from some of the congenital immunodeficiency diseases. Shannon and Ammann have suggested that the presence of hypergammaglobulinaemia and human immunodeficiency virus (HIV) antibodies, together with deficiencies in the cellular immune response, strongly support the diagnosis of AIDS,[1] but hypogammaglobulinaemia with a negative antibody response could, in some cases, be one of the first manifestations of the immunological abnormalities produced by the viral infection.

## Case reports

The first patient was born in 1983 by caesarean section because of maternal isoimmunisation; gestation was 32 weeks and he weighed 1800 g. He had an exchange transfusion on day 1 and another transfusion when he was 1 month old. When he was 5 months old he was admitted to hospital because of failure to thrive, respiratory distress, persistent oral candidiasis, and diarrhoea. Results of laboratory tests showed disseminated cytomegalovirus infection and hypogammaglobulinaemia. When he was 6 months old the diagnoses of severe combined immunodeficiency and sex linked hypogammaglobulinaemia were refuted by a normal lymphocytic response to phytohaemagglutinin and the presence of B and T cells in his blood (Table); he was treated with intravenous gammaglobulin. There was no family history of immune deficiency. He continued to have recurrent bacterial infections and candidiasis and excreted cytomegalovirus. He died

Table *Immunological data on the two patients and their blood donors*

| | *Case No 1* | | *Blood donor* | *Case No 2 (age 4 months)* | *Mother (donor)* |
|---|---|---|---|---|---|
| | *(at 6 months)* | *(at 16 months)* | | | |
| Lymphocytes/platelets | Normal/normal | Normal/40 000 | Normal/normal | Normal/normal | Normal/normal |
| Immunoglobulins | | | | | |
| IgG (g/l) | 1 32 | 6 90 | 19 70 | 0 95 | 21 50 |
| IgM (g/l) | 0 92 | 1 18 | 1 38 | 0 28 | 1 75 |
| IgA (g/l) | 0 16 | 0 30 | 2 96 | 0 12 | 3 48 |
| B cells (%) | 12 | 0 | 16 | 17 | 14 |
| T cells* (%) | | | | | |
| T3 | 42 | 36 | 65 | 21 | 49 |
| T4 | 30 | 28 | 14 | 11 | 21 |
| T8 | 28 | 46 | 59 | 25 | 43 |
| T4/T8 index | 1 2 | 0 6 | 0 2 | 0 4 | 0 5 |
| Phytohaemagglutinin response index† | 27 | 2 | 43 | 18 | 21 |
| Pokeweed mitogen response index† | 6 | 4 | Not done | 3 | Not done |
| Circulating immune complexes (%) | Negative | 50 | 18 | 21 | Not done |
| Anti-HIV antibody (ELISA) | Negative | Negative | Positive | Negative | Positive |
| Western blot | Not done | Not done | Positive | Negative | Positive |
| Anti-cytomegalovirus antibody titre | 1/128 | 1/64 | 1/512 | Negative | Negative |

*Indirect immunofluorescence with monoclonal antibody (Ortho), mean (SD) normal values—$T_3$=60 (8%) $T_4$=42 (6%), $T_8$=21 (5%), †normal values PHA index >20, PWM index >1 0 ‡normal values <15%

at the age of 16 months, at which time he weighed 5·5 kg and was cachectic. The donor of the blood used for the transfusion was a homosexual positive for HIV antibodies with obvious immunological abnormalities (Table).

The second patient was born at 36 weeks' gestation with intrauterine growth failure weighing 1900 g. He had a blood transfusion at the age of 1 month for anaemia, his mother being the donor. At the age of 4 months he was admitted to hospital with diarrhoea, persistent oral candidiasis, fever, respiratory distress, quadriplegia, and hypertonia. Results of laboratory tests showed hypogammaglobulinaemia and abnormal lymphocyte subpopulations (Table). Candida was isolated from blood and cerebrospinal fluid. Computed tomography showed severe cortical atrophy and calcification of the basal ganglia (Figure). The electroencephalogram was normal, but the brain stem auditory evoked potential was abnormal. He was given gammaglobulin intravenously, but at the time of writing he had repeated bacterial infections. He weighed 5·2 kg at the age of 11 months and was severely retarded. His father was a drug addict and both parents were positive for HIV antibodies. The Table shows the mothers immunological data.

## Discussion

The fact that the lymphocytes from both patients initially responded to mitogens and produced IgM and that T and B cells were found, together with the progressive deterioration of the immune responses, indicates that neither had severe combined immune deficiency or agammaglobulinaemia. Both were at high risk of AIDS having had contaminated blood transfusions early in life, and the mother of the second patient was seropositive.[2]

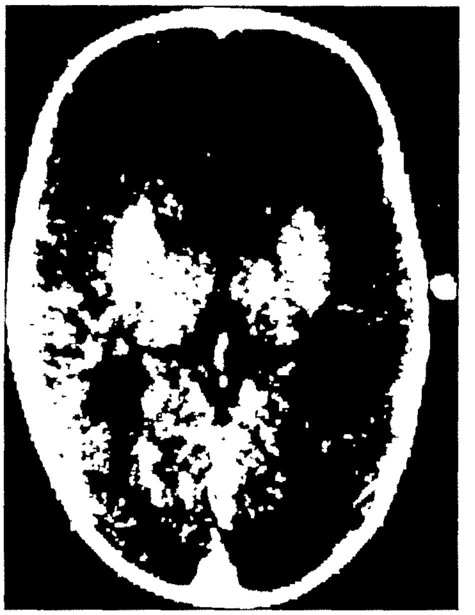

Figure *Computed tomogram, case no 2 showing cortical atrophy and small calcification.*

One of the differences between infantile and adult AIDS is the high incidence of bacterial infections in the former. Abnormalities of T lymphocytes are usually found in the blood of patients with AIDS, but recently abnormalities of B cell function have been described both in adults and children.[3] Hypergammaglobulinaemia is more common than hypogammaglobulinaemia.[4]

A 9 year old boy with clinical and laboratory findings consistent with a diagnosis of AIDS has been described, with an atypical antibody response to HIV.[5] He had raised concentrations of immunoglobulin in his serum and had survived disseminated cryptococcosis, suggesting that infection was by a different retrovirus. In contrast, the blood donor of our first patient and the mother of the second had positive antibodies diagnostic of HIV infection by Western blot analysis.

An immature immune system associated with prematurity could have a bearing on the severity of the B cell abnormalities in our two patients; prophylaxis and treatment with gammaglobulin should be considered for such patients.

Neurological abnormalities have been reported in patients with AIDS.[6] Cortical atrophy and calcification on computed tomography are common findings, but in future culture and identification of the virus will have to be done to confirm the diagnosis.

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## *Current topic*

# The disability of short stature

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Few paediatricians would deny that children with extreme short stature face a disability that may affect their physical, psychological, and social well being. Though considerable research has been performed on the nature of this disability, it has been focused on patients who are very short, secondary to conditions such as growth hormone deficiency or achondroplasia, and are attending specialised clinics. Increasingly, however, children are being referred who represent the extremes of normal variation in growth and physical development. They do not have a pathological condition and yet their parents are seeking medical advice, usually at their own instigation or at the suggestion of their family doctor, friends, or relatives. Though some individuals, such as Napoleon, are said to have been spurred on to greatness (or infamy!) by their small size, it is widely assumed that short stature, even within the normal range for the population, represents a disability and with the recent availability of treatment with biosynthetic growth hormone this assumption requires further study.

This review will examine the evidence available on the disability of short stature, which to date is based almost entirely on 'pathological' short stature It will then summarise the relevance of these studies to 'short normal' children.

### Studies in children with extreme short stature

A variety of diagnoses are represented, of which growth hormone deficiency is the commonest In all the studies, however, short stature was the main medical problem.

**Psychological/social features.** Being unusually short would seem to have an adverse effect on psychological and social well being. High incidences of behavioural disorders have been found[1,2,3] and particular characteristics identified. Of these, social isolation and lack of appropriate aggressive drive are perhaps the most prominent.[2,4–7] Usually, the level of interaction with children is determined by assessment of their age based on their physical appearance; in short children, age tends to be underestimated, and this can lead to the child being 'infantilised' by parents, peers, and teachers.[1,4] In response the child may adopt babyish behaviour or become a 'mascot' figure.[2,8] Depression,[1,8] low self esteem,[4,5,7] poor social coping,[6] and an increased incidence of somatic complaints[5] are also described.

Though adolescents may fare worse than younger children, the published works are inconsistent about the effect of sex on the problems of short stature. This may partly reflect the small numbers and the variety of diagnoses within and between studies as growth hormone deficiency is commoner in boys and Turner's syndrome occurs only in girls Some studies have shown a higher incidence of personality or behavioural disturbances in adolescent girls,[6,9] while a psychoanalytic approach suggested that problems might be worse in adolescent boys,[8,10] the latter being supported by clinical referral patterns. Abbott *et al* found no differences in emotional functioning between the sexes.[1]

**Intellectual function.** In some conditions in which short stature is a part, such as fetal alcohol syndrome, low intelligence quotient (IQ) and retarded development are described features. In most cases of short stature, however, distribution of IQ is within the normal range, and mean scores for study groups approximate to that of the general population.[1,3,6,11] Some authors have found lower scores on testing particular areas—for example, visual motor integration[1] and spatial orientation,[6] but others have noted no differences in subscores.[3,11] The heterogeneity of the diagnostic groups might have accounted for the high incidence of low IQs in a few small samples and Turner's syndrome is associated with poorer non-verbal performance and difficulty in spatial orientation, which is likely to affect samples containing this diagnosis.

**School achievement.** Early studies showed scholastic underachievement with discrepancy between IQ and academic functioning.[3] Steinhausen and Stahnke[6] noted, however, that IQ and grade achievement were similar in their case and control groups but that children with short stature of unknown aetiology were more likely to be at a lower grade than expected for their age. In another small sample Abbott *et al* found that five of 11 children with growth hormone deficiency had been retained at least one grade but that in four the reason given was absenteeism caused by admission to hospital and poor academic achievement was usually associated with low IQ.[1]

A short longitudinal study of school achievement has been performed recently. In 1982 the achievement of 56 children attending a growth clinic for short stature of varying aetiology was assessed. All children had at least average IQ, but 32% had repeated a grade and their parents usually cited immaturity and small size as the reasons, with no reports of scholastic underachievement. Two years later (1984) the children who had repeated a grade (adolescent girls and young boys were most likely to have been retained) were retested; they still showed lower academic achievement and were functioning at a less than appropriate level for their current grade, despite their retention. Specific questioning of parents now revealed that they could accurately assess their child's academic abilities yet had previously (1982 survey) blamed the problems of short stature for grade retention.[9 12]

School functioning is also affected by interaction with teachers and peers. Short children may be subject to special treatment at school, often being overprotected and treated as if younger than their actual age and this in turn can lead to underachievement.[13] In the studies of Holmes *et al* described above teachers and parents thought that short children had appreciable adjustment problems, and in the group that had repeated a grade teachers (but not parents) thought there were more personality and behavioural disorders.[9 12]

Once again, the heterogeneous nature of the small groups studied may confuse the issue as many patients had either growth hormone deficiency (which may be associated with central nervous system disorders) or short stature of unknown aetiology (many syndromes involving retarded development are also associated with short stature) Normal intelligence but scholastic underachievement, however, is a recurring theme

**Adult attitudes.** The way in which parents perceive and subsequently handle the problems of their short children is critical to the child's own adjustment. Denial of the child's problems has been noted, with overestimation of his present and future height;[1 4 8] this may lead to severe disappointment with response to treatment with growth hormone.[14] Parents often thought that their child wished to be 'babied', but children's adjustment and maturity were better if they had been treated by their parents at an age appropriate level.[2 4] Commonly perceived problems were teasing by peers[1 9] and a younger sibling overtaking the child in height.[1 8] Perhaps as a consequence, parents sometimes exhibited overprotective or compensatorily lenient behaviour, while possibly reinforcing the infantilism by their own actions.[4 5]

Interaction with other adults is also important and the perceptions of teachers have been mentioned previously. The tendency to treat children at a size appropriate rather than age appropriate level is emphasised by the study of Rotnem *et al,* in which it was noted that specialist medical and nursing staff involuntarily treated the children with growth hormone deficiency as if they were younger than their actual age, despite theoretical awareness of their problems.[4]

### Studies in adults

Like studies in children, observations on adults have been made almost exclusively on clinic attenders with extreme short stature, usually secondary to bony dysplasias (especially achondroplasia) and growth hormone deficiency.

Various problem areas have been identified among adults with achondroplasia. Marriage was less common than in the general population and if achieved was sometimes associated with other problems such as minor psychiatric disorders, suggesting that it was not always a supportive relationship. Although employment was generally found, many thought that they had had to overcome considerable prejudice to obtain and maintain their jobs. Those with achondroplasia felt stigmatised but employed various socially compliant coping mechanisms, such as humour, to deal with this, and few personality differences were found between them and standard populations. Where they existed they were usually 'acceptable' traits, such as increased extraversion and conformity, and scores for anxiety, neuroses, and hostility were normal.[15 16]

Adults with growth hormone deficiency showed similar characteristics to those with achondroplasia in the sample of Brust *et al,*[15] but Clopper *et al* found an increased incidence of abnormalities.[17] Adults with growth hormone deficiency had inertia of libido, and deficient socialising and pair bonding behaviour, with depression and other behavioural disturbances being much more prominent than in those with achondroplasia. Canadian adults with growth hormone deficiency who had received growth hormone as children had normal educational attainment but lower rates of marriage and employment than the general population and were socially isolated. These disadvantages were not clearly related to the response to treatment [18]

## Psychological effects in children at the extremes of normal variation

So far the evidence presented had considered patients who are so short that their stature could be considered pathological A much larger group consists of those individuals whose growth patterns represent the extremes of a wide normal variation. Little research has been conducted in this population, with the notable exception of the studies of Mussen, Jones, and Bayley.[19–21] Though their data was collected in the 1930s and '50s, they are interesting because of the long follow up period into adult life. They took a sample of adolescents attending a normal school and selected the 20% who were earliest developing in puberty and the 20% who were latest, following them longitudinally from 12 to 17 years. The two groups were also recontacted when they were in their early 30s [19–21]

The selected difference between these two groups was the tempo of puberty, but as this has a direct effect on height the late maturing group had heights in the lower part of the normal range (10th–25th centiles) and the early maturing group in the upper part (60th–90th centiles). The results showed considerable differences between the two groups. Late maturers had high scores on measures of negative self conceptions, inadequacy, dependence, rejection, and disturbed relationships with parents Early maturers scored high on self confidence, independence, and dominance. Trained observers also rated the groups differently; they judged early developers to be more physically attractive, relaxed, matter of fact, and less affected and late maturers to be more expressive and eager (often in a childish way), tense, and with attention seeking mannerisms (though this may have been as much a difference in the observers' attitudes as in the boys' behaviour)

Many subjects were contacted again when they were in their early 30s, by which time the differences in their physical appearance were extremely small (height difference ½ inch) The two groups were found to be very similar in their social characteristics—for example, marriage, children, income, education—but the psychological differences noted during adolescence had essentially persisted into adult life Those who had been early maturers scored high on socialisation dominance, self control, and responsibility, while the late maturers were less dominant, wished for more support, and tended to be rebellious but non-assertive.

## Implications for growth hormone treatment

The handicap associated with extreme short stature led to vigorous attempts to find a suitable treatment. The isolation and preparation of human growth hormone provided hope for children with growth hormone deficiency but was not thought to be useful in other conditions or in normal short children. Extraction from pituitary glands severely limited supplies and few clinical trials could be carried out. In the past few years, however, small series have suggested that growth hormone might be used to increase growth in normal short children and that up to 50% of children with genetic short stature or constitutional growth delay might respond to treatment.[22]

There remain several unknown factors. Firstly, availability of human growth hormone has limited trials to low dose regimens and there is virtually no data on the effects or side effects of higher doses. Secondly, practical considerations have limited duration of treatment (usually 6–12 months) and so we do not know how long treatment should continue. Thirdly, no prospective method of distinguishing responders from non-responders has been found. Lastly, the crucial issue, the effect of treatment on final adult height cannot be addressed for many years. The question of who should have growth hormone has been reviewed recently[22] and discussed by an ad hoc committee of paediatric endocrinologists representing the American Academy of Pediatrics. The committee maintained that the only established indication for treatment with growth hormone was growth hormone deficiency and that its use in all other cases must be considered experimental. Furthermore, they considered that the handicap associated with short stature might be due to underlying emotional disturbances and so might not be relieved by treatment with growth hormone and concluded 'if it ain't broke, don't fix it'.[23] The prevailing negative attitude to short stature in Western societies and the ethics and philosophy of treatment with growth hormone in short normal children was also extensively discussed in a Hastings Center report three years ago.[24]

The recent development of commercially viable biosynthetic growth hormone products means that the supply of growth hormone is theoretically unlimited, although the cost of the preparation is high. This paves the way for increased clinical use but also potential abuse, both of which were anticipated and discussed at an international conference held in 1983.[25] It was expected that paediatricians would come under parental pressure to prescribe growth hormone and one consensus opinion was that 'much of that pressure will come from parents whose children are not fulfilling parental expectations in competitive sports, social interactions and academic achievement.'

While to be very short is clearly disabling psychosocially as well as physically, we know much less of the effect of having a growth pattern at the extreme of the normal range. An increasing number of patients seeking specialist medical advice for short stature, however, belong to this latter group; presumably they feel disabled and many are anxious to have treatment that will make them taller. Aside from the diagnostic difficulties[22] and therapeutic uncertainties, the nature of this disability poses additional questions. Are these children experiencing an abnormal psychological reaction to a physiological growth pattern? If so, they are probably not representative of the short population at large and might be helped by counselling in addition to or instead of treatment with growth hormone, particularly as it will be impossible to guarantee a favourable outcome from treatment with growth hormone. Psychological disturbances may be created as well as alleviated by treatment. Overexpectation of treatment by both parents and their children with growth hormone deficiency has led to great disappointment and feelings of failure, despite a medically acceptable increase in growth rate.[7 10 14] Some children have found adjustment to the unusual experience of growing difficult, with aggression and depression becoming prominent, while pre-existing traits of low self esteem and depression were not relieved and were sometimes aggravated by treatment.[2 7] In the Canadian series 21% of patients needed psychiatric or psychological counselling during treatment with growth hormone.[18]

An alternative answer may be that these normal short children seeking medical advice represent a vast number in the community, whose short stature is disabling but who, for various reasons, have not sought or had access to medical care. Included in this number may be children who are short secondary to another medical problem, such as cystic fibrosis or renal disease. We do not know how much of an additional burden this places on them or of what benefit treatment with growth hormone may be. In this alternative scenario the large numbers of children who may be helped by treatment with growth hormone emphasise still further that its careful allocation and evaluation is essential for the benefit of the individual child and the whole community.

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*Personal practice*

# Pitfalls in developmental diagnosis

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SUMMARY I have never seen a paper or chapter of a book devoted to pitfalls and mistakes in developmental diagnosis. This paper is designed to try to fill the gap. It concerns the avoidance of mistakes in developmental diagnosis and is based entirely on mistakes that I have made myself and now learnt to try to avoid and on mistakes that I have seen, most of them repeatedly. I have made no mention of mistakes that could theoretically be made but that I have not personally seen.

I believe that most assessment errors are due to overconfidence and to the view that developmental diagnosis is easy. Many other mistakes are due to reliance on purely objective tests with consequent omission of a detailed history and physical examination, so that factors that profoundly affect development but are not directly related to the child's mental endowment are not weighed up before an opinion is reached.

It is a mistake to think that developmental diagnosis is easy and requires little training. It often is easy, but it may be extremely difficult. Errors cause much parental anxiety and may be tragic for the child.

Failure to recognise a normal variation in some aspect of development may lead to unnecessary investigation or treatment, worry for the parents, and disadvantage for the child. The common cause of erroneous dogmatic statements about development is overconfidence.

I know of no article on pitfalls in developmental diagnosis apart from a brief discussion in the third edition of Gesell and Amatruda's 'Developmental diagnosis' [1]

## General principles

I believe that certain general principles must be observed if pitfalls in developmental diagnosis are to be avoided. They are as follows.

(1) An essential requirement is a thorough knowledge of the normal (better termed the average) and the normal variations that do not amount to disease and an effort to try to understand the factors that cause these variations. A thorough knowledge of the normal is a necessary preliminary to the study of disease.

(2) Children differ widely in all aspects of development—so widely, that it is impossible, despite the claims of some workers,[2] to define the range of normal. It would be convenient if the range of normality could be delineated, but it is impossible. A line can never be drawn between normal and abnormal. All that can be said is that the further away from the average a child is in any field the less likely he is to be 'normal'. Failure to recognise this leads many to declare that a child 'should' reach milestones, such as sitting unsupported, walking without help, talking, or controlling the bladder, by a specified age, as if all normal children are the same, with no normal variations. Such views, relayed to parents after developmental assessment, may cause great anxiety. I have heard of parents being told that their 6 month old baby has 'failed' his test and of 8 month old babies being referred to psychiatrists because of suspected lateness in passing certain milestones.

(3) A child's level of development is the end result of a wide variety of factors—prenatal, perinatal, and postnatal. Many of these are not directly related to the child's mental endowment yet have a profound effect on his development. Failure to take these factors into consideration helps to explain the poor correlation so often reported between psychological tests in infancy and later intelligence quotient (IQ) scores, the assessment having been made solely on the basis of objective tests.

(4) The mentally subnormal child, unless the

subnormality is of later postnatal origin, is retarded in all aspects of development, except sometimes in gross motor skills, and rarely in sphincter control. Hence we can never diagnose mental subnormality on backwardness in just one or two fields of development.

(5) Some fields of development are far more important than others for developmental assessment. The least important in infancy is the most easily scored—namely, gross motor development (sitting and walking). Some mentally subnormal infants show average motor development, while advanced motor development certainly does not signify a high level of intelligence.[3] The most important features for the assessment are features that cannot readily be scored because norms have not been established, features that Gesell termed 'insurance factors'—the child's alertness, responsiveness, interest in surroundings, persistence, concentration, and the glint in the eyes. Other features are his memory, understanding, and the quality of his vocalisations (which is difficult to assess without special equipment).

Manipulative development is far more important than gross motor development. Important developmental features, rarely seen in case notes, include ambidextrous (average 20 weeks) or unidextrous (average 28 weeks) approach to an object, the rapidity with which he accidentally drops a cube, the question of whether he drops one cube when offered another, tremor or ataxia or other abnormal hand movement when reaching for an object, the transfer of a cube from one hand to another (normally 6 months), and the quality of the grasp (evolving from the crude palmar grasp of the cube at about 5 months to the mature grasp between the tip of the thumb and the tip of the forefinger at 11 to 12 months).

The index finger approach to an object is an important and easily observed feature from 9 to 10 months of age. If I see the index finger approach to an object I would think that the child's *overall* mental development could not be less than that of a 9 to 10 month baby The 'pincer grasp', by which one means the grasp of a pellet or small object, refers only to the grasp between the tip of the thumb and tip of the forefinger; it develops at the same time as the index finger approach. so does the 'matching' of cubes—the child apparently comparing the cube in one hand with that in the other. When he holds out a cube to his mother, it is noted whether he withdraws it (average 44 weeks), refusing to let it go, or shows the later skills of releasing it into her hand (average 48 weeks). It is not enough to record just *whether* a child has acquired a certain skill: one has to note the maturity and the rapidity with which he does it. For instance, in the crude screening test for hearing, it is noted not only *whether* he turns his head to sound, but the *rapidity* of the response, and his later ability to turn to sound made below the ear, or later still above the level of the ear.

It is thoroughly misleading to obtain a score for different aspects of development, as in the Griffiths tests,[4] obtain the average, and then regard that as the 'IQ'. Failure to recognise the different developmental importance of various aspects of development again helps to explain the relatively small correlation between psychologists' tests in infancy and subsequent IQ scores.

(6) A clinical developmental diagnosis should always be based on the history, full physical and developmental examination, special investigations where relevant, and the interpretation of the results. The diagnosis must be made on the child as a whole. It is a mistake to make it purely on the basis of examination of one little bit of the child by a few objective tests in a limited field of development: such an approach inevitably omits vitally important facts. Neither should it be made as a 'spot' diagnosis. It is usually easy at a glance from a distance to diagnose Down's syndrome and some other forms of mental subnormality, but it is difficult for parents to accept a doctor's 'spot' diagnosis, followed by his confident statement on the outlook.

It is easy to be misled by a child's ugliness, odd facies (often taking after one of his parents), charm, facile conversation (in the case of hydrocephalus), difficult behaviour, or isolated advancement or retardation in one field.

## The history

To avoid mistakes by the omission of relevant, highly important factors that affect development, a detailed history is essential. It will include all prenatal, perinatal, and postnatal factors. These will cover the main 'risk' factors in pregnancy, such as infections, placental insufficiency, hypertension, antepartum haemorrhage, adverse socioeconomic factors, malnutrition, genetic and familial factors, and drug taking, including drugs of addiction. It will include in particular factors associated with the aetiology of mental subnormality and cerebral palsy. The importance of these risk factors must not be exaggerated—a matter of importance when a child's suitability for adoption is being considered. When there is doubt about his level of development the history of a risk factor, such as mental subnormality in a parent, serves only to increase that doubt. But a risk factor itself should never lead to a hasty diagnosis that a child is mentally subnormal. A mentally subnormal parent can have a normal or mentally superior baby.

The family pattern of development is important, particularly with regard to backwardness in motor skills, speech, sphincter control, or learning disorders or to backwardness in early weeks followed by normal or advanced development.

If serious mistakes are to be avoided appropriate allowance for the history of preterm delivery must be made If the baby was of low birth weight the duration of gestation must be known to distinguish intrauterine growth retardation. The Griffiths and other developmental tests do not make such an allowance. Whereas an average full term baby begins to smile in response to his mother's overtures at 4 to 6 weeks, the baby born three months early would be expected to smile at 4 to 6 weeks plus 3 months. I have seen babies born two or three months early assessed for adoption 6 weeks after birth.

Few would fail to obtain a history of perinatal 'risk' factors, but these factors are often misinterpreted.[5] It is a widespread practice to ascribe mental subnormality or cerebral palsy to 'brain damage' or 'birth injury' due to hypoxia or breech or forceps delivery, without considering the possible or likely prenatal causes of those conditions. I recently reviewed this subject, pointing out that cerebral palsy commonly occurs after normal labour, with no perinatal problems, while severe delivery problems, including pronounced hypoxia, are usually not followed by evidence of 'brain damage'.[5] Failure to recognise prenatal factors as the main cause of so called 'brain damage' has major medicolegal consequences and results in errors of counselling about the risk of future pregnancies

The history must include postnatal factors that may profoundly affect development and that are unrelated to his mental endowment For instance, defective weight bearing in an otherwise normal baby is usually due merely to his not being allowed to bear weight on the legs, for fear that he will develop rickets, bow legs, or knock knee. Yet some tests—for example, Ruth Griffiths—ignore this and give a low score as a result. Other aspects of parental management, stimulation or lack of it, socioeconomic problems, emotional deprivation, and the chance given the child to learn to feed himself, dress himself, and attend to his toilet needs need to be known. It is important to know if the mother is out at work all day The paediatrician must know about malnutrition, illness, head injury, exposure to toxic substances, symptoms suggestive of cerebral palsy—for example, the hand or hands being kept tightly closed at an age when the hands should be largely open or asymmetry of limb movements as in hemiplegia

Precision in history taking is necessary if errors are to be avoided. It is essential that parent, doctor, or nurse should understand exactly what the other means. The doctor, on the basis of his experience, has to decide how reliable is the history and how much of it he is able to accept It is a mistake not to ask the mother about her child's development: the reliability of her story must be checked against the doctor's own objective findings. It is not enough to ask whether the child smiles, rolls over, grasps objects, sits, creeps, walks, talks, or is 'dry'. It is not enough merely to know *whether* a child does a thing, but *when* he began to do it, and how often, and with what degree of maturity.

Developmental histories that I experience are commonly of very limited value because they are imprecise. The milestone 'beginning to smile' refers only to smiling in response to the mother's overtures and not to a grimace or twitch when she tickles the face or to the baby's facial movement in sleep. 'Rolling over' refers to rolling *completely* over, and rolling from prone to supine has to be distinguished from rolling from supine to prone, which usually comes later. 'Grasping objects' means going for an object without it being put into the hand and has to be distinguished from the grasp reflex, or the ability to hold an object placed in the hand 'Sitting' means sitting on the floor or another hard surface for seconds, either with the hands forward for support or without support. It does not mean sitting with support in the pram. 'Creeping' (on hands and knees) has to be distinguished from the earlier 'crawling' on the abdomen. 'Chewing' has to be distinguished from 'sucking'—for example, a biscuit. 'Walking' means walking a few steps without support; 'talking' consists of saying words with meaning, not just 'mumum, dadada'. 'Toilet trained' means that the child is mainly dry and clean day and night and has to be distinguished from the much earlier conditioning when the child voids as the buttocks feel the rim of the potty, whether awake or asleep. If control is incomplete the stage reached should be recorded—for example, the child telling the mother that he has voided, or, later, that he is about to void.

I commonly see in notes 'held her head up' at x weeks or 'bears weight on the legs'. These words are meaningless without definition. Newborn full term babies can hold the head up momentarily or bear some weight on the legs Other information needed concerns the age at which the child began to play games and to have skills involving imitation and memory—for example, peep-bo, clap hands, waving 'bye-bye', helping to dress by holding the arm out for a sleeve or foot out for a shoe, and feeding himself by picking up an ordinary cup, drinking from it, and putting it down without help and without much spilling.

A properly taken history includes the *rate* of development, indicating that the rate is steady, improving, or slowing, vital information necessary for assessing a difficult case.

### The physical examination

For developmental assessment, a full physical examination is essential if serious errors are to be avoided. This will include examination for neurological and physical handicap, congenital anomalies, and defects of vision and hearing—all conditions that may profoundly affect development and developmental tests but that may have no direct relation to the child's level of intelligence. Due allowance for these handicaps must be made, for otherwise his real ability and potential may be seriously underestimated. A physical disability that is easily missed in a child who is later than usual in gross motor skills is Duchenne muscular dystrophy: the diagnosis is complicated by the lower than average level of mental development commonly found.

An essential part of the physical examination is the head circumference in relation to the child's weight. Serial measurements are essential if there is doubt, for they may show a falling off from the centile distribution, which is a most important indication of brain defect. Other causes of unusual head measurements, such as familial traits, must be known. I myself made a mistake in measurement by using a tape measure that had become inaccurate by stretching.

Irrelevant physical features include the age of closure of the anterior fontanelle, an epicanthus, or central palmar crease; the latter may be found in normal children.

During the physical examination general features are noted, such as unusual behaviour (as in autism), the quality of vocalisation, the child's interest in surroundings, and responsiveness, and signs suggesting mental subnormality, such as bruxism when awake, persistence of 'hand regard' after 20 weeks, or mouthing, slobbering, and casting at an age when he should have grown out of it.

### The developmental examination

Whatever the developmental test, it must be ensured that the child's performance seems to be the best of which he is capable. He should not be tested when he is on drugs or is tired, sleepy, poorly, hungry, or bored When he does badly in a test a decision has to be made about whether he was really trying. The older child may refuse to take part in a test because he is shy or regards it as too easy or just silly.

I think that it is a mistake to separate the infant or small child from his mother. It adds to the difficulty of the child not achieving his best in strange surroundings. The mother has to resist the urge to help the child in the tests. Rigid adherence to a method of testing is undesirable: the tester should adjust the order of tests as soon as he sees that the child is not interested or is becoming bored. One never corrects a child or says 'no' when he performs a test incorrectly.

In a busy obstetrics hospital follow up clinic or a child health clinic tests must be practical. I know a book that describes 115 different methods of testing, occupying up to 125 minutes for each child. Other popular tests take 40 minutes or more.

I feel that some do not sufficiently distinguish that which is interesting—for example, many of the 70 or more primitive reflexes—from that which is important. As far as I can determine, the only primitive reflexes that can help in diagnosis are the grasp reflex, Moro reflex, and asymmetrical tonic neck reflex. Some would add the oral and parachute reflex. It is useful to ask how a particular test would help the diagnosis and what condition would be missed by not doing it.

Once a test has been chosen—for example, as described by Gesell or anyone else—the materials used must be the same as those on which the norms were established. I often see children tested with cubes of varying sizes, whereas Gesell's norms were based on one inch cubes.

### Interpretation

It is said that intelligence tests are more a test of the intelligence of the examiner than the examinee The examiner must allow for all factors, including physical and sensory handicap, which greatly affect development, especially when they have little to do with the child's mental endowment. Cultural and ethnic factors may considerably affect a test score, but there is no satisfactory way of allowing for them except by judicious guesswork.

I often see incorrect interpretation of a test because extenuating factors have been missed. For instance, a 3 or 4 year old's poor performance on repetition of digits may be due to a hearing defect or failure to understand what he is asked to do. A poor performance on motor or other tests may be due to hypotonia, hypertonia, a visual defect, or mere lack of opportunity to practice—for example, weight bearing.

A 6 or 8 week infant placed in the prone position will revert to the fetal position if asleep and may be given a low score as a result. Advanced development in the prone position may be due to cultural factors,[7] the child having been encouraged to lie and sleep in that position.[8] Other causes of delayed motor development are often missed—familial traits personality (fear of falls). shuffling, or Duchenne muscular dystrophy It is usually a mistake to ascribe late motor development to obesity or a dislocated hip. Delayed sitting may be due to congenital shortening of the glutei, gastrocnemius, and hamstrings.[9] A poor performance in drawing tests, or in identification of pictures, may be due to the child not having been given a chance to learn Many ascribe delayed toilet training purely to psychological problems, ignoring the familial factor, delayed maturation of the relevant part of the nervous system, the sensitive period for learning, or urinary tract infection or anomalies. Psychological problems may well be superimposed on other factors, without being the primary cause.

An important source of error is the popularity of a unitary score in developmental assessment and misinterpretation of its accuracy and predictive value. Knobloch and Pasamanick have rightly deprecated this [1] They discussed the confusion concerning the terms 'developmental quotient' (DQ) and 'intelligence quotient' (IQ). The DQ indicates how far a baby has progressed in *all* aspects of development, especially behaviour, in relation to the average for his age. The IQ relates his age to his performance, mainly in verbal and problem solving tests, on the basis of pass or failure. The DQ is profoundly affected by the environment and many other factors unrelated to his genetic endowment.

No one has satisfactorily defined 'intelligence', but many would agree that it cannot be described as a single score or figure, for there are many different types of intelligence and of human abilities.

It is unwise, especially in the young infant, to give an exact figure for a test score. I was asked to see an older child with a learning disorder: he had been seen by two psychologists, who independently reported an IQ of 79 and 79.1. An 'exhibit' in a clinical meeting showed that a 6 week old baby with a metabolic defect had an 'IQ' of 70 on the Griffiths scale and at 12 weeks had an 'IQ' of 76—conclusive proof of the efficacy of treatment! Such accuracy is impossible. One reason is the fact that the so called 'norms' of development, on which most of the commonly used developmental tests are based, were established on a highly selected population, instead of on the population as a whole. I briefly reviewed this matter with reference to the developmental tests described by Gesell, Beintema, Brazelton, and the Denver and Kansas Groups.[10] The tests were based only on children of white origin who were full term and mostly had no prenatal or perinatal risk factors, such as breech delivery, socioeconomic problems, or those thought to have any developmental abnormality. It follows that we have no valid norms with which to compare the development of children not satisfying these criteria and accuracy is impossible.

When, as often happens, there is much scatter in a child's development in different fields I pay particular attention to Gesell's 'insurance factors'—the alertness, responsiveness, and interest that the child shows—even though he is backward in many or even all fields of development. I believe that I am less likely to err if I pay more attention to his positive achievements, those skills (other than gross motor development) in which he does best, than to the negative ones in which he is most retarded.

In making his assessment of the child's potential the doctor has to try to decide whether backwardness in various fields has been due to adverse environmental factors, such as illness or emotional deprivation, how much is related to physical handicap, and how much is potentially reversible.

There are important pitfalls to avoid in the interpretation of signs that may sometimes indicate cerebral palsy, mental subnormality, and visual or hearing defects. Cerebral palsy cannot be diagnosed on the basis of isolated retardation in motor development nor on the basis of exaggerated tendon jerks (in the young baby) or even persistent ankle clonus, for those signs may disappear as the baby gets older. There is constant confusion about the plantar responses in the first year or so: they are flexor unless there is disease of the pyramidal tracts Excessive extensor tone is readily missed, and I have made the mistake myself. It is a highly important pointer to cerebral palsy. The infant seems to have good head control in ventral suspension and in the prone position but gross head lag when pulled up from the supine to the sitting position. Resistance is felt when pulling him up to the sitting position because of spasm of the erector spinae, glutei, and hamstrings; the knees flex, so that he cannot sit with the legs extended; he may tend to rise on to his legs, wrongly suggesting good motor development; and each time he is seated leaning forward he falls backwards

I have made the mistake of diagnosing adductor spasm, on account of limited abduction at the hip, when the limited abduction was due to muscle contracture due to the hypotonic child constantly lying in one position, and I diagnosed the spastic form of cerebral palsy on account of limited joint extension, when the correct diagnosis was punctate epiphyseal dysplasia.

Minimal involvement of the upper limbs, as seen when the child is going for cubes or building a tower, is easily missed, so that spastic paraplegia is diagnosed when the correct diagnosis is spastic diplegia. Spastic paraplegia should alert the doctor to the possibility of a spinal lesion rather than a cerebral one. Spastic monoplegia is extremely rare: I saw only one possible case in my personally observed series of over 750 cases of cerebral palsy.

Toe walking is often thought to be due to cerebral palsy when it is only a normal variant or is due to rarer causes, such as congenital shortening of the Achilles tendon, Duchenne muscular dystrophy, unilateral hip dislocation, autism, or dystonia musculorum deformans Spastic children are often wrongly thought to have a 'mixed' form of cerebral palsy because the characteristic awkwardness and splaying out of the hands is thought to be athetosis.

I have often seen a late walker thought to have the ataxic form of cerebral palsy because shortly after first walking without support he is unsteady on his feet—like the younger child when he walked alone at a much earlier age. Delayed walking in a mentally normal child is commonly no more than a familial feature: it is most unlikely to be due to congenital dislocation of the hip and almost certainly not due to obesity.

I have often seen infants thought to be blind, because of delayed eye following, when the delay was due only to mental subnormality: in the same way I have seen mentally subnormal children thought to be deaf, because of delayed response to sound. Delayed visual maturation[11] is a rare cause of apparent blindness: but the absence of nystagmus or abnormal ophthalmoscopic findings in the presence of otherwise normal development would avoid the mistake of diagnosing mental subnormality.

Isolated delay in speech is never due to mental subnormality. In a mentally normal child the commonest cause is a familial trait; deafness is a less common cause. It is not due to tongue tie, jealousy, or 'everything being done for him' Every child learns the meaning of words long before he can articulate them, and some have learnt the meaning of scores of words without being able to articulate any. The common lulls in the development of speech when a child is learning to walk are a common cause of anxiety.

## Conclusion

After a full history, physical and developmental examination, and interpretation of the findings it is possible to say much about a child's developmental potential and something about his talents but not to say what he will do with them. That will depend on many factors in the future—the quality of his home, friends, and school, his personality, health, and nutrition, and the opportunities that he will have.

Developmental assessment can be very difficult. The wise doctor will learn from mistakes, and to avoid pitfalls in the future, he will try his best to follow up all children presenting unusual developmental features—and there are many of them

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## *Personal view*

# My enuresis

I was dry up to the age of 4½ when I started at primary school. I was at the school a week before the enuresis trouble started. It all started off when I was refused permission to go to the toilet at the time in which I needed to go urgently. At the time I was refused permission to go I tried to go to the toilet and I was stopped. I tried to go three to four times and still I was stopped from going Then in the end I gave up and I just sat down and cried. The feeling got very strong to go to the toilet. I tried again, but still I was refused Then all of a sudden I found myself wet. At this age I was not able to understand what had happened. Then the following week I was allowed to go once in the morning and once in the afternoon But still I was being wet during the day. Then it started on a night as well for being wet At the age of five I was still being wet Then I was made to sit on one chair with my name on it.

When I look back on this it makes me angry to remember that I was made to sit on one chair only, and it was drummed in to me that it was my chair. In my mind that is wrong. If anything it does not help matters at all. If anything it makes matters worse. This helps young children to be nasty to others with problems. With this I was started to be picked on by class mates. The name calling started I was getting called 'pissy arse', 'smelly bitch' and other names related to wetting. Through this constant name calling I started to withdraw myself from the rest of the class At breaks and lunchtimes I just sat outside the classroom and cried my eyes out. I did not know why I was crying or I was unsure whether it was out of self pity or anger. After I got into the next class up I was allowed to go to the toilet but was still withdrawn. The bad habit of just wetting myself had set in. I still carried on being withdrawn for the rest of my primary school days.

By the time I had finished primary school my bladder control was gone. The picking on me carried on, and was getting worse. At this time I was wetting during the day four to five times, and every night the bed was wet

At the age of 10 I saw a doctor. I was also seeing NSPCC officers with the doctor. I had medicines, star charts, and a few bed alarms. These really had no effect after a few days of use Then I saw a doctor at the hospital There I had a few x-rays taken The NSPCC officers helped out with financial matters, talking through problems, and helping the family through a depression with my dad being made medically retired, for my dad had been medically retired since I was 4½. We hardly were getting Christmas presents. Still I was getting picked on because of the wetting trouble.

At this time I started to feel sorry for myself which did not help matters one bit I had become emotionally disturbed. I felt extremely timid. The wetting was not getting any better, neither was it getting any worse

When I started the modern school the wetting was still occurring. After a couple of months, being at the modern school, one of the teachers started to spray the room every time I left to take the register When I approached the teacher, who was my form tutor, I was not really pleased; if anything I lost my temper over the matter. This was sorted out. But still the wetting continued and so did the name calling. I was still trying to stop being withdrawn. One of the teachers started to try and help me.

I was very emotionally distressed. Anybody could snap at me and I would just break down and cry my eyes out I would say that I was reduced to a bundle of nerves. I was still being wet. The cruelness of other children still continued. I was going to have to toughen up or I would not be able to stick up for myself I thought it was about time I stopped people from being the bullies they were This was when I started smoking to help me release the pain of hatred against the whole of the school

I only started to smoke because I just could not bring myself to talk to anybody about this trouble The trouble continued all through first and second years of the new school. Now as well as being called 'pissy arse' and 'smelly bitch', I was also getting told that I only got a bath three times a year This got me really vexed. When I answered the bullies back I got blamed for starting the trouble in lessons.

In the third year the name calling got less for a month or two, then it all started up again just as bad as before I hated the whole school including my friends (the few that I had). The name calling got a bit too much, until one day at lunchtime I walked out of school just so I had time to think things over. Even if I could talk to the teachers, I was sure that they would understand or even give a sympathetic ear for a few minutes.

Even after I had walked out of school all the headmistress could do was shout and ball. This had me reduced to tears Then I found the courage to snap back to get to speak. Then I was slapped across the face and told to get out the school. When I refused and asked quietly if I could discuss with her why, I walked out of school. Then she was willing to sit down and listen to what I had to say on the matter.

I was still being wet during the day and night time. I have to admit that I was a bit smelly, but even when I was wet I was being told off. I was getting very vexed about this. Some people just cannot give way to be nice to people with problems, instead of constant torment from nasty children at the school

Then in the fourth year I was only at school from 5 September to 8 January, but on 10 January I had to go to an adolescent unit This time I was not having a light time because while I was in the adolescent unit I was getting behind with work, which became a pressure. I was still being wet for the first two months. Then after that I was not wet very often Mind you it was a centrally heated establishment. The staff seemed to treat me as if I was four to five years old. If anybody had been stubborn through the day they were not allowed any sweets after school or they were sent to bed without supper. In my opinion this was a childish way to treat 13, 14, 15, and 16 year olds. It would have been better if they had talked over why they were being stubborn. Then there was the meetings at 7 o'clock to discuss problems, but nobody would speak up.

I suddenly found the wetting was back, but then it went all over again. The torment at least stopped, but only until I went back to my original school For only six months I was dry so I discharged myself in August 1985. Then I went back to school. That's when all the name calling started again I was dry for six weeks then the wetting started up all over again I was really disappointed with myself. I started seeing a child psychologist in October. This was a great help because I was able to get troubles off my mind. The wetting had decreased in the day time but was still happening at night. Then I was discharged from him in August 1986. At this time I had enrolled at the grammar school.

At home I was really on edge and some of the time, or should I say practically all the time when I came in from walks or bike rides I was really in a trouble causing mood. This was not like me at all.

I was always getting on people's nerves, but I was still being wet which was a help for being irritable. Now that I was at the grammar school those who went to the other school with me made me feel as if I did not really fit into the certificate of prevocational education course.

The staff at the grammar school were really more friendly and also treated me as if I was an adult. I found and made a new friend, Sharon My best mate made me feel that I could get on and ignore trouble and just get on with my work. I soon found out who the trouble makers were. I still could not and would not make friends with the lot from my other school

## Analysis

At the beginning if I found that I had a child that had the enuresis trouble, this is what I would do to try and help the child to discard the enuresis trouble as follows:

For a start I would see if the child was warm enough during the night. If not, I would install an electric fire or I would install radiators if I had the money. This would keep the bedroom warm and aired. Also every night I would put on an electric blanket on the bed if I possessed one, either that or I would place a hot water bottle in the bottom of the child's bed. For another alternative I would put an extra blanket or two if I had none of the things mentioned above.

For the day time, I would try to make sure that the child was warm enough during the day I would make sure the child had a vest and petticoat under the clothes. Also warm woolly socks or tights. If I had the money I would make sure that the child went to school with clean, warm clothes on every day and also had a bath or a shower each and every morning and night to stop the smell of urine. I would also buy some medicated talc to put in the child's pants to prevent soreness from uric acid.

If this did not work to discharge the enuresis, I would take the child to the doctors to get some medicines to see if that would help with the problem. And if that did not work I would go to the hospital to have a urine sample done. Then have an $x$-ray done on the kidneys, ureters, bladder and urethra. If the problem is left too long the trigone valve may go wrong so if the $x$-rays showed no signs of disorder this is what I would do·

Start retraining the child to go to the toilet regularly and that would have to be done every hour and a half. Then increase the time spaceage. The child should not be shouted at or refused access to the toilet The teaching staff should always be told all about this kind of trouble. All teaching staff should not shout or show self pity at the child But if the child has an accident at school the child should be shown what to do so that she knows if she wets at school again. The child should take some spare clothes and be able to wash her clothes out straight away and they should be dried for her.

If a child is worried about anything and cannot talk to her parents, she should be able to talk to the teaching staff or ask a member of staff to get in touch with someone who understands a child's mind or just someone for the child to talk things over with in confidence

This may help to solve the trouble of enuresis, but I would never give the child a star chart, bed alarm, or even a count down alarm. These would start to get the parents tired and very impatient. I think there could be more better help financially to claim for sheets and clothing.

If the parents are really interested in helping children with enuresis, please stop and think what the child might be going through. Or try to imagine how you would feel if it was you who had, or has, the enuresis trouble. Then you would not allow your children to be inconsiderate towards other children with problems.

*Editor's note*: the author, aged 16, is now dry during the daytime and has only occasional wet beds. She is hoping to train as a nursery nurse.

*Archives of Disease in Childhood,* 1987, **62,** 869–871

# Correspondence

## Vasoactivity of the major intracranial arteries in the newborn child

Sir,

I read with interest the paper of Drayton and Skidmore, showing vasoactivity of the cerebral circulation in preterm infants[1] I note in their study population four infants had developed intraventricular haemorrhage and five infants had signs of periventricular leucomalacia Volpe has shown with positron emission tomography that intracranial haemorrhage has a dramatic effect on regional cerebral blood flow,[2] and it is well recognised that intracranial haemorrhage can cause arterial spasm Previous studies have shown that intraventricular haemorrhage occurs soon after birth in many infants [3] [4] It is possible that the changes in cerebral vasoactivity that Drayton and Skidmore describe in their paper are secondary to intraventricular haemorrhage. If the results of the nine infants with either periventricular haemorrhage or leucomalacia are removed from the preterm study population, do the results reported still pertain? If so this makes a much more interesting paper.

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Dr Drayton comments·

Dr Beverley enquires whether the changes in cerebral artery calibre reported in March 1987 could be secondary to intracranial pathology. The nine infants with abnormal real-time ultrasound scans were heterogenous for both type and timing of abnormal appearance. When these infants are removed from the analysis the same results pertain In the remaining 21 infants, mean ACA velocity increased from 2·5 to 5·5 cm/second, mean MCA velocity increased from 4·8 to 8·8 cm/second There was no significant change in head and neck perfusion and the mean standardised flow·velocity ratio decreased from 19·5 to 8·5

These changes are clearly not the result of intracranial haemorrhage, but the implied early vasodilation is more likely to be a factor in its genesis.

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## Cardiovascular effects of tolazoline and ranitidine

Sir,

Tolazoline, used in standard doses, reliably produces gastric erosions and bleeding The article by Bush *et al*[1] suggests that ranitidine should not be used to counteract this undesirable side effect. For the past seven years we have used 2·8% sodium bicarbonate stomach washouts to reduce bleeding from erosions caused by tolazoline In full term infants we use 10 ml of this solution to wash out the stomach every two hours until the bleeding stops, and subsequently, at longer intervals. Usually 1–2 ml remains in the stomach each time. We have had no problems with hypernatraemia to date, although most infants develop a mild alkalosis Bleeding usually stops or is greatly diminished within 24 hours

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## Management of asthma in schools

Sir,

Hill, Britten, and Tattersfield's views on the management of asthma in schools and Dr Couriel's letter, suggesting that the school medical service could help to identify the underdiagnosed and undertreated,[1] [2] spur me to enlighten them on the school doctor's role. Every mother seen in the small group of schools where I work is asked if their child has any relevant symptoms. If asthma is diagnosed this is fully discussed with parent and child and types of treatment outlined If the diagnosis is new or if treatment administered so far is ineffective such information is passed on (*most politely*) to the family doctor. There is rarely a response. When the child is next seen at school, one is told that: (i) the cough/wheezing is better or; (ii) that it persists with or without treatment, or; (iii) 'my doctor says this isn't asthma' Thus identification of asthma in school is easy, improving treatment is more difficult

With regard to the three questions asked by Drs Hill, Britten, and Tattersfield:

1 How well are schools informed about children with asthma? This varies greatly. The question then is who should tell whom? School medical officers do not see children in this area until the term after school admission, furthermore, they are well advised on confidentiality of medical information. It would be confusing and unhelpful if the school doctor were to tell the school that a child has asthma, especially if parent or family doctor is unwilling to accept this diagnosis Such a problem is not insoluble but takes time and tact

2 How much access should children have to inhalers? The answer should surely be an individual one depending on many factors such as age, reliability, capability etc. Unfortunately, there have been schools where headteachers disallow any treatment in school or insist on mothers coming to school to administer it. It is to be hoped there is now a more considerate view

3 Should teachers be given instructions in managing childhood illness? For asthma this would be generally useful but such advice appears to attract interest mainly from those personally involved with asthma and those teaching the very young.

In conclusion, there is undoubtedly a need for much more widespread education on asthma and your Journal is to be congratulated on having four articles on this subject in the April issue

Meanwhile, one continues to try to spread the word as 'that school doctor'

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# Autosomal dominant polycystic kidney disease in children

Sir,

Taitz *et al* refer to autosomal dominant polycystic kidney disease (ADPKD) in children and the value of the family history in its diagnosis.[1] Their observation is in accordance with our experience in the cooperative study on cystic kidneys of the *Arbeitsgemeinschaft fur Padiatrische Nephrologie* We know about 49 children with ADPKD, including cases with 'Potter sequence', as well as children with only slight ultrasonographic changes without any renal impairment. The authors' conclusion, drawn from the bimodal distribution of the age at detection of previously published cases, which postulates two distinctive groups is not without problems. As the authors admit themselves, childhood cases may be underreported Complete ascertainment of a great number of children at risk is necessary; and rare cases with enlarged kidneys should also be detected There are at least six possible explanations for early onset, of which Taitz *et al* mention only two (1 and 2)

1 Homozygosity for ADPKD is unlikely because, as the authors mention, there are no reports of children with early signs both of whose parents have ADPKD

2 Cases of early manifestation might be due to a specific genotype. The authors favour the hypothesis that children with grossly enlarged kidneys are either compounds for the gene of the autosomal recessive (ARPKD) as well as of the autosomal dominant variety, or that they are heterozygous for both mutations at different loci

3 Early clinical signs could be part of a spectrum of severity, ranging from cases with grossly enlarged kidneys in newborn infants to children who don't show any symptoms until adulthood. Age at onset might then show a unimodal distribution due to a polygenic background, as is known from Huntington's chorea.[2]

4 One possibility could be the existence of 'modifying alleles' at the same gene locus[3] to explain rare pedigrees of spinal muscular atrophy [4] The critical study would be to screen systematically a large number of children at risk for ADPKD, starting at birth, or even prenatally A bimodal distribution of age at onset would strongly point to the existence of specific genotypes, either due to compounds or double heterozygosity, where the frequency of the second mode would even permit an estimate of the prevalence of the responsible gene(s).

5 Although unlikely because of transmission through both affected fathers as well as affected mothers, sex related modifying influences should also be considered as occurs in early onset cases of myotonic dystrophy

6 Rare exogeneous factors (infections, nutrition?) should also be considered

Despite the so far unknown nature of early manifestation of ADPKD in children the observation of familial cases should be taken into account in genetic counselling

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KLAUS ZERRES *and* PETER PROPPING
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## Dr Taitz comments

Zerres and Propping suggest a number of alternatives to those we put forward to attempt to explain the number of cases of adult polycystic kidney disease presenting in the newborn period with renal masses, and the apparent paucity of such reported cases in older children We agree that it is essential for larger groups of 'at risk' children to be followed up from the newborn period into adolescence before a clear explanation will emerge for this phenomenon Unfortunately, the current literature contains several isolated reports of cystic disease in older children, but few family or population studies which throw much light on this question

Although we have our own favourite hypothesis at present, we would not wish to give the impression that we think that the various alternatives, including those suggested by the writers can be discounted, quite the contrary. We did consider the proposition that there might be a specific allele, but then one would have expected that the affected parent would have had renal masses from birth We have now increased the number of offspring of children who have one parent with APKD to over 40 but have still not found an older child with kidney masses It may be that only by pooling resources from a number of centres will an answer to this intriguing question emerge

L S TAITZ
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# Transient congenital hypothyroidism

Sir,

Danziger, *et al*[1] report a case of a transient hypothyroidism (seven months) in a girl whose mother used povidone iodine preparation during pregnancy. They emphasise that the newborn infant had hypothyroidism as a result of exposure to iodine used topically by her mother They base their hypothesis on the fact that the iodine crosses the maternal skin and loads the immature thyroid gland which becomes saturated Hormonogenesis is suppressed (Wolff Chaikoff process). After the age of 7 months the iodine loading probably stops and the thyroid hormonogenesis returns to normal. The authors did not prove the iodine overload, however, and they do not report the results of measurements of maternal or neonatal total blood iodine concentrations or ioduria The permeability of skin and the effect of iodine loading vary [2]

In 1978 I already recommended that 24 hour urinary iodine excretion should be measured in cases of transient hypothyroidism of the newborn.[3] I emphasised that a common and apparently harmless practice—that is, disinfecting the skin with iodine—results in a profound hormonal disorder, which is dangerous for a neonate Although this is reversible, thyroid disorder induced in the first days or weeks of life is not necessarily without long term effects [2]

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## British paediatrics

# Hospital medical staffing

The Health Departments, the Joint Consultants Committee, and the Regional Health Authority chairmen have issued a consultative document, *Hospital Medical Staffing: Achieving a Balance,* which makes proposals for bringing the hospital staffing structure into balance over the next 10 years

In its response to this document the British Paediatric Association (BPA) points out that paediatrics is now a district based specialty with responsibilities in both hospital and community. New arrangements for manpower must therefore include general paediatricians, paediatric specialists, and paediatricians working in the field of community child health. The BPA is currently undertaking a comprehensive survey of paediatric manpower which will be made available to the Joint Planning Advisory Committee and will provide accurate up to date information on present staffing levels and future needs. This will assist the review of registrar and senior registrar numbers in paediatrics and indicate districts where posts should be located.

The BPA is concerned that the number of registrars and senior registrars should be sufficient to enable research to be undertaken in clinical departments and to take account of the present expansion in community paediatrics. Experience in community paediatrics will become an essential part of training for paediatric registrars

The increase in the number of senior house officer (SHO) posts to allow for a breadth of training is obviously welcomed. The BPA believes the average time in this grade is likely to rise to four years, of which one year will be undertaken in one of the medical specialties before part I of the MRCP diploma is obtained. Many SHO's in paediatrics will seek careers in other disciplines—for example, accident and emergency medicine and general practice—and others will undertake careers in general and community paediatrics The number of paediatric SHO's must take these training needs into account. The regional advisers in paediatrics should be seen as the official source of career advice for SHO's contemplating a career in paediatrics

The proposed new non-training intermediate grade with entry from SHO level may prove attractive, particularly to doctors working part-time because of family commitments, and would be suitable for those interested in school medicine. The BPA, however, foresees only a limited role for this grade in providing long term on-call duties for acute paediatrics.

At present, few district hopitals and not all supraregional services have the number of supporting staff to provide a minimum safe level of 24 hour emergency cover—the so called 'safety net'. The recommendation that acute services should have three or four intermediate level doctors is clearly welcomed for paediatrics, but in view of the specialised nature of acute problems in children it will often be impossible to allow cross cover from other specialties even at SHO grade.

The overseas doctors training scheme in which district registrar posts are to be reserved for overseas doctors in training is fully supported by the BPA.

The BPA would like the opportunity of discussing various aspects of these manpower proposals in relation to paediatrics. The Association through the regional representatives on its council is well informed and is in a unique position to advise on the future staffing trends in paediatrics.

A D M Jackson

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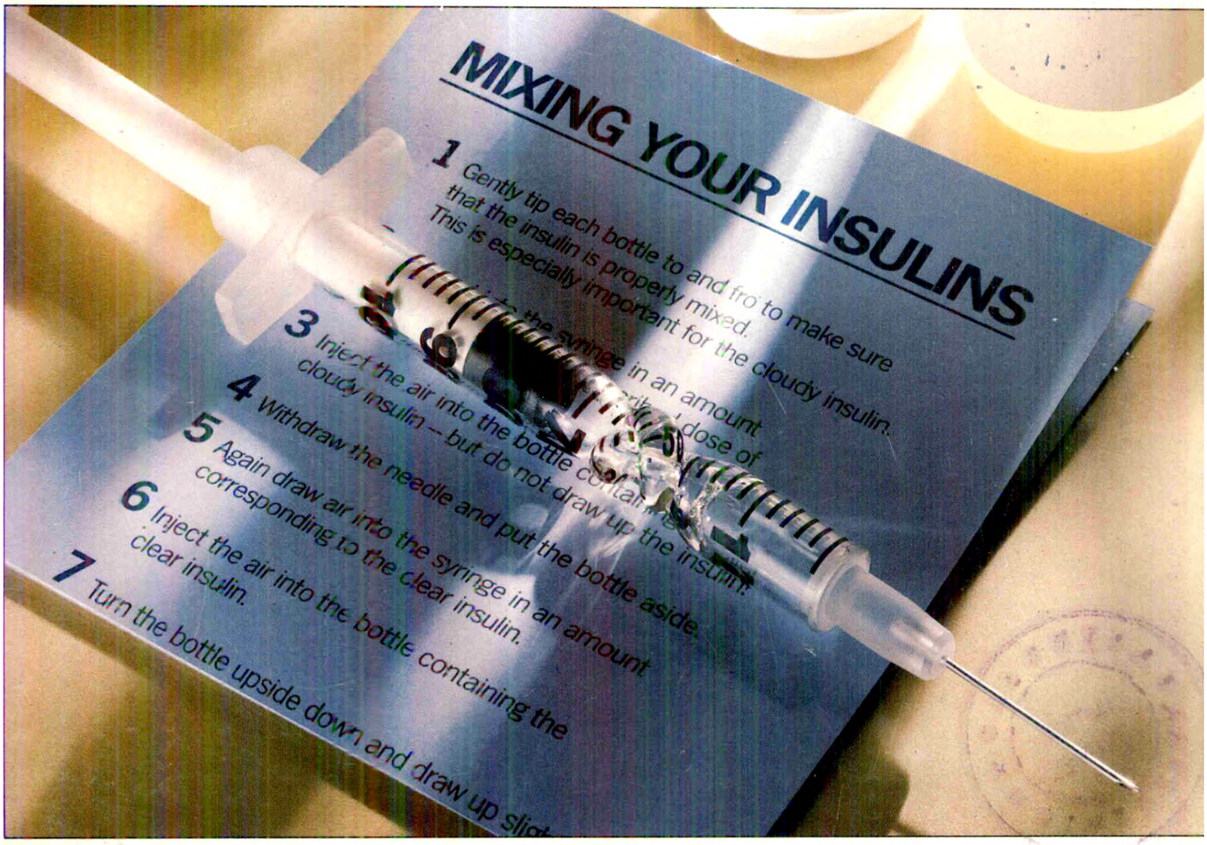
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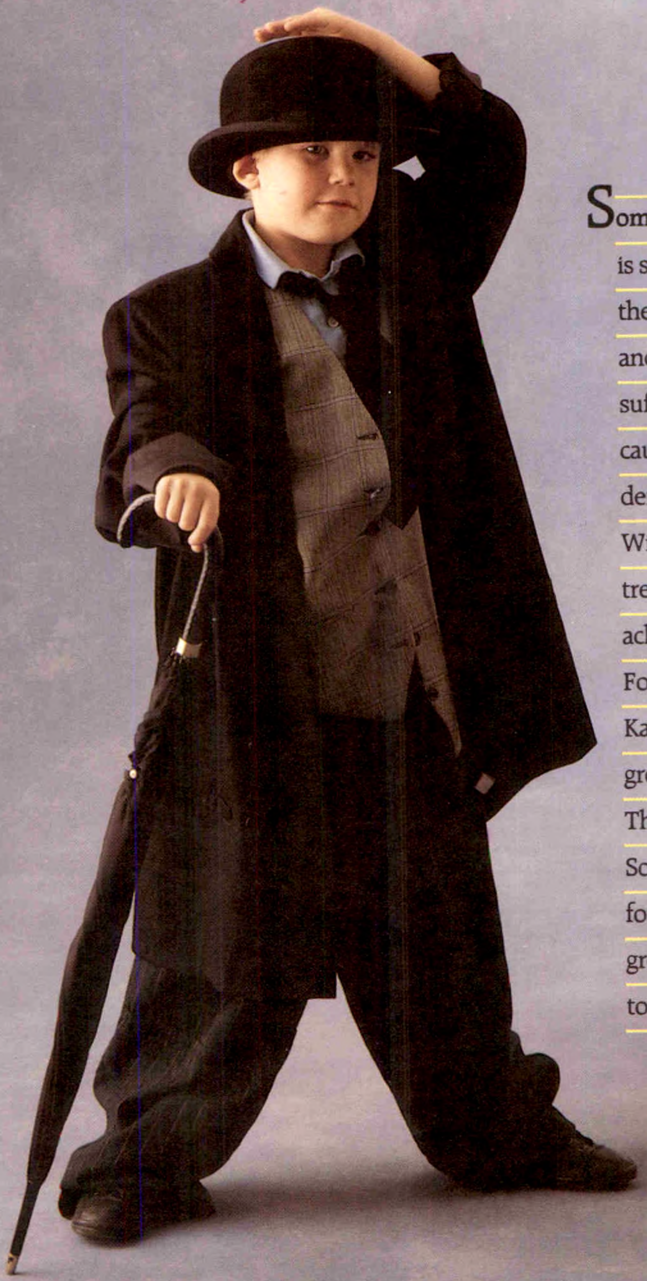

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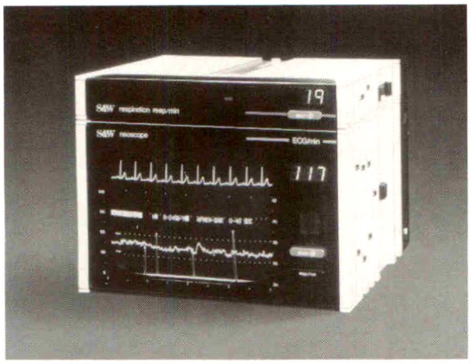

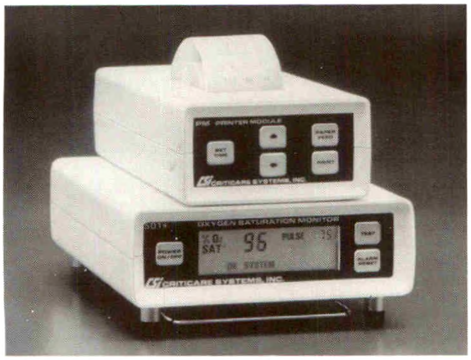

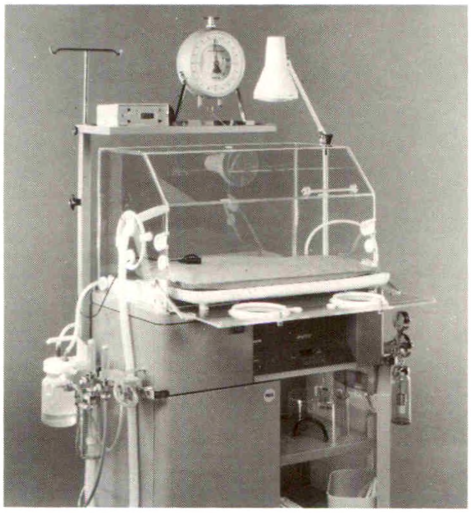

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*r 20kg:* 20mg/kg of body weight per day:
vere cases may be increased up to
g/kg/day. Increases above this only if
na valproic acid levels, clinical chemistry
haematological parameters can be monitored.
**bined Therapy** It may be necessary to raise
ose when used with anticonvulsants which
ce liver enzyme activity. Dosage of
iturates should be reduced if sedation is
rved. Optimum dosage is mainly determined
eizure control and routine measurement of
na levels is unnecessary. **Contra-indications,**
**nings** *Contra-indication:* Active liver disease.
*effects:* Liver dysfunction including hepatic
e resulting in fatalities has occurred in patients
se treatment included valproic acid or sodium
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ders, organic brain disease or severe seizure
ders associated with mental retardation. The
ents mainly occurred during the first 6 months
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onvulsant therapy. Clinical
toms are more helpful than
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s of hepatic failure. The onset of
ute illness, especially within the
months, which may include
toms of vomiting, lethargy or
ness, drowsiness, anorexia, jaundice
s of seizure control is an indication
mediate withdrawal of the drug.
nce to date does not establish which
tigation could predict this possible
se effect; measurement of liver function
d be performed in the first 6 months of
py in those who seem most at risk and those
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*Archives of Disease in Childhood*, 1987, **62**, 873–875

## *Annotations*

# When not to do a lumbar puncture

> It may seem a strange principle to enunciate as the very first requirement in a Hospital that it should do the sick no harm
>
> FLORENCE NIGHTINGALE
> *Notes on Hospitals*, 1859

There are three reasons for not performing any clinical investigation (1) its inconvenience, discomfort, or expense is disproportionate to its clinical value; (2) it is unlikely to produce clinically useful information; or (3) it is unjustifiably dangerous. Any one of these considerations may apply to lumbar puncture. I do not, for instance, authorise a lumbar puncture for a toddler who seems perfectly well after a febrile convulsion, though I am eager to do so if there is any clinical doubt or in a very young child There are many occasions (such as in most cases of epilepsy) when lumbar puncture is unlikely to give information that is sufficiently important to justify the assault on the child. Such a decision is easy, however, compared with deciding whether a lumbar puncture is or is not too dangerous When the child is not critically ill there is little problem. Any symptoms or signs which could suggest an intracranial lesion or raised intracranial pressure will be investigated by computed tomography before lumbar puncture is considered, for example, suspicious headache or vomiting, ataxia, or hemiparesis Symptoms of Guillain-Barré syndrome or subacute sclerosing panencephalitis, however, might justify lumbar puncture without tomography, but the only urgent indication for lumbar puncture is the suspicion of bacterial meningitis.

### Lumbar puncture in meningitis

Until recently the need for lumbar puncture in diagnosing meningitis was accepted almost without question.[1] In September 1985 the *British Medical Journal* published a letter from Dr J R Harper describing a child with meningococcal meningitis whose condition deteriorated rapidly two hours after lumbar puncture and who subsequently died He asked whether it was permissible to avoid lumbar puncture if the clinical diagnosis of meningitis seemed clear. The editor asked four experts to comment; two (a paediatrician and a physician) accepted that if there was a clear clinical diagnosis treatment should be given and lumbar puncture avoided, and two (a paediatrician and a microbiologist) thought that diagnostic lumbar puncture should be routine.[2]

In subsequent correspondence[3-5] most writers considered that treatment of meningitis without lumbar puncture was indicated, at least in some circumstances, and there was guarded support for this approach in Australia.[6] A recent comprehensive review from the USA advocated withholding or delaying lumbar puncture when there were signs of raised intracranial pressure, when there was serious cardiorespiratory disease, or when the skin over the puncture site was infected [7] Some paediatricians have reported the successful treatment of meningitis without lumbar puncture.[8]

**Why do a lumbar puncture?** Reasons given for retaining routine lumbar punctures are: to confirm the diagnosis, to identify the organism, to test for antibiotic sensitivities, and to rationalise the treatment of contacts in the case of meningococcal or haemophilus meningitis.

Paediatricians differ about the reliability of the clinical diagnosis of meningitis. Blood culture identified the organism in over 80% of the cases due to *Streptococcus pneumoniae* or *Haemophilus influenzae* at the Birmingham Children's Hospital, but failed to do so in over half of the cases due to *Neisseria meningitidis*.[9] Organisms may be identified from smears from skin lesions, but the reliability of this method has not been determined.

What important diagnosis might be missed by not doing a lumbar puncture? Intracranial tumour and acute encephalopathy, such as Reye's syndrome, have been mentioned as differential diagnoses,[3] but for neither is there an indication for lumbar puncture If herpes encephalitis is suspected acyclovir should be given, antibody titres to herpes virus measured, and electroencephalography and computed tomography carried out.[10] Spontaneous subarachnoid haemorrhage may be difficult to diagnose, but the acute onset, fundal abnormalities, focal neurological signs, and absence of signs of infection would usually point to the correct diagnosis without the need for early diagnostic lumbar puncture.[1] In a young child intracranial injury may be a possibility, but again lumbar puncture is not indicated. Intracranial abscess must always be considered, whether or not the cerebrospinal fluid is infected and tomography or radionucleotide scan carried out. Clear fluid might intensify a search for metabolic disease, but the blood glucose concentration should always be checked; serum concentrations of calcium, magnesium, ammonia, and amino acids, and toxicological analysis of urine or blood may also be indicated.

Not doing a lumbar puncture means that the clinician will need to maintain a greater degree of diagnostic alertness over a longer period Treatment with chloramphenicol will usually be adequate in meningitis caused by one of the usual three organisms,[11] so identifying the organism in the cerebrospinal fluid is not absolutely essential. Resistance to chloramphenicol is rare, and a change of antibiotic will be dictated by lack of clinical response rather than by in vitro sensitivities. Prophylaxis for contacts is often advised for cases of meningococcal or haemophilus meningitis Most haemophilus infections and about half of those due to meningococcus will be identified from blood cultures.[9] If not, cultures of nose and throat swabs may indicate which contacts should be given rifampicin. Abandoning routine lumbar puncture would result in a loss of important epidemiological data, especially about meningococcal disease, but such a consideration will not weigh heavily with the clinician faced with an individual sick child

**The reasons for not doing a lumbar puncture.** The main reason for not doing a lumbar puncture for suspected meningitis is the fear of transtentorial or transforaminal herniation or coning. We all accept that this can occur and may prove fatal, but can we estimate the risk and can we define the circumstances in which the risks outweigh the benefits?

Coning results from raised intracranial pressure caused by either cerebral oedema or acute hydrocephalus and may occur even if a lumbar puncture has not been done. Because for many years lumbar puncture was mandatory in meningitis however, most cases of coning have followed lumbar puncture, so it is not possible to know how many would have happened anyway. Signs may develop soon after lumbar puncture and it is likely that the lumbar puncture can only make the coning worse. While it may be wise to withdraw only a small amount of fluid at diagnostic lumbar puncture, the amount is not critical because however carefully it is done fluid may continue to leak through the punctured meninges after the procedure.

Williams *et al* in 1964 described six children with bacterial meningitis and signs of brain stem compression, two of whom showed a dramatic improvement after treatment with hypertonic urea given intravenously.[12] They gave no estimate of the proportion of their children with meningitis who developed coning.

Horwitz *et al* examined the records of 302 children admitted to hospital in Cleveland, Ohio, with bacterial meningitis Coning was suspected clinically in 27. Ten children died, three of whom had had signs of coning. Many of those with coning diagnosed clinically improved after treatment with mannitol and dexamethasone, but 27% of the survivors had severe neurological damage. The authors could not identify any features on presentation that would have predicted the likelihood of coning[13]

Slack found evidence of coning in six of the 90 deaths from meningococcal infection in all age groups in England and Wales in 1978.[14] One of the patients had not had a lumbar puncture, but in three meningococcal meningitis had been diagnosed before lumbar puncture. In Glasgow at least five of 11 deaths in 248 children with bacterial meningitis were thought to have been associated with brain swelling and coning,[15] and in a recent six month period two children with coning after lumbar puncture for meningitis were referred to the intensive care unit of the Hospital for Sick Children, Great Ormond Street.[16]

There is evidence, therefore, that coning may contribute to the outcome in an appreciable number of deaths from bacterial meningitis—perhaps 30% or more. It is difficult to predict which children are at particular risk, although signs suggestive of raised intracranial pressure, such as impairment of consciousness, recurrent vomiting, or focal neurological signs, would raise suspicions Fundal signs of raised pressure alone are not adequate, but further evidence of incipient coning would make lumbar puncture a foolhardy procedure. Such signs include deterioration in the conscious level, decerebrate or decorticate rigidity, tonic seizures, unilateral or bilateral fixed dilated pupils, loss or paresis of ocular movements, hemiparesis, apnoea or irregular respiration, and extensor plantar responses. Measures to reduce intracranial pressure should be taken immediately coning is suspected.

## A personal approach

In the past it was my policy to insist on lumbar puncture for all children suspected of having meningitis. I shall continue to do so for a very young child who has had a febrile convulsion or for one who does not rapidly recover and for a child with an acute feverish illness when the diagnosis is uncertain but meningitis is a possibility.

I shall consider treatment without lumbar puncture when the diagnosis of meningitis seems clear and the child is seriously ill, has a typical purpuric rash, has fundoscopic evidence of raised intracranial pressure, has impaired consciousness, has other signs of incipient coning, or has been ill for several days.

The debate will continue, but any decision about lumbar puncture must be made by an experienced doctor.

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# Steroid scare

Some children with asthma and eczema are being deprived of steroids because of fear of side effects. The result is undertreatment, particularly of those most severely affected. The consequences of this may be worse than the potential known side effects.

## The need for inhaled steroids in chronic asthma

The idea that prophylactic inhaled steroids are a last resort is wrong. They offer effective management of asthma for many patients whose symptoms are not controlled by antigen avoidance regimens, bronchodilators, inhaled cromoglycate, or regular slow release theophylline. There should be no hesitation in using inhaled steroids for patients not controlled by bronchodilators or cromoglycate, and persistence of bad attacks, frequent symptoms, or unstable twice daily peak expiratory flow readings warrant prompt treatment with inhaled steroids. Some children are managed for years on large quantities of bronchodilators alone, and repeated requests for bronchodilators should suggest that prophylaxis is required. The underdiagnosis of asthma is now well known, but the problem of undertreatment is less well appreciated

## The safety of inhaled steroids in asthma

Although 80–90% of an inhaled dose of steroid is swallowed, it is deactivated in the liver before reaching the systemic circulation Regular inhaled steroids in therapeutic doses are remarkably free of unwanted systemic effects, such as growth impairment [1 2] Indeed, relapse of pre-existing atopic eczema or allergic rhinitis is a common problem when changing from systemic to inhaled steroids. Only the question of whether inhaled steroids cause a minor degree of adrenal suppression is unresolved. A report of salivary cortisol concentrations showed no evidence of suppression,[3] whereas another study reported low nocturnal and early morning plasma cortisol concentrations,[4] although the clinical relevance of the latter study is doubtful.[5 6]

## Short courses of oral steroids for acute asthma

Failure of the patient with acute asthma to respond promptly to treatment with bronchodilators is an absolute indication for treatment with steroids. Short courses of steroids are effective and safe,[7 8] but the optimal dose and duration of such treatment is not known. Even a single large dose has been shown to be beneficial in adults,[9] but most children are likely to need three to seven days of treatment. Studies of deaths from asthma both at home and in hospital have repeatedly shown that steroids were not given, which was usually combined with a failure to appreciate the severity of the attack.[10–13] Some patients die too early in an unexpected attack for steroids to be effective, but while there can never be proof that others would have survived had they received steroids, at least some would probably have done so. The decision to prescribe oral or rectal theophylline instead of short courses of oral prednisolone, when maintenance treatment with bronchodilators, cromoglycate, or steroid aerosols, or both, have already failed, may be a recipe for disaster. Similarly, while the increasing use of nebulised bronchodilators at home has brought benefits, some children are exposed to the real hazards of delayed referral to hospital and arrival in a moribund state[14 15] because a poor response has gone untreated [16]

## The need for maintenance oral steroids in severe asthma

The efficacy of prophylactic inhaled steroids may lead one to forget that there are a few children with severe intractable asthma who can only be adequately controlled with regular prednisolone or adrenocorticotrophic hormone (ACTH) The temptation to wean patients off regular steroids—for example, when they are sent to residential schools—can be catastrophic. An unpublished survey of 109 British asthmatic children who had been sent to the Swiss alps reported that most were taken off steroids, but at follow up a few years later seven had died. There are two great dangers with this policy: one is that, although children with asthma often improve when sent to a residential school, they are liable to relapse on returning home for holidays; the other is that after being weaned off long term oral steroids, recovery of a normal hypothalamo/pituitary/adrenal axis response to stress may take as long as a year, and throughout that period the life of a child with chronic asthma is constantly at risk.[17] It is worth remembering that suppression of the hypothalamo/pituitary/adrenal axis is far less when prednisolone is given in the early morning rather than in the evening. Adverse effects, especially hypothalamo/pituitary/adrenal axis suppression and growth inhibition, are greatly reduced when oral steroids are given in the morning and only on alternate days. The theory that the adverse effect of ACTH on growth is reduced has not been confirmed.[18] This, combined with the need for injection, now means that ACTH probably has a lesser role in the management of severe atopic disease When long term systemic steroids are used, cataracts may develop.[19] Children with severe eczema are considerably more likely to develop cataracts than those with asthma, but this is usually not connected with the administration of steroids

## Topical steroids for atopic eczema

Treating eczema is quite unlike treating asthma, and far more complicated. The price for undertreatment of severe atopic eczema is disfigurement and handicap; the penalty for overtreatment with steroids is similar. With long term topical steroids, the major worry is skin atrophy, but with careful treatment of facial eczema this complication should not be troublesome.

The different strengths of topical steroids cause confusion among doctors and parents alike. A good example of such a muddle was seen when a two month old infant with a facial rash was prescribed beclomethasone dipropionate (category II, potent) When this was unsuccessful, 0·5% hydrocortisone was prescribed, but the mother declined to go to the chemist because she knew hydrocortisone was, 'far too strong'.

There are some rules:

**1 Communication.** Fear of using safe, mildly potent, topical steroids is a cause of needless suffering. Most parents have the idea that topical steroids are dangerous. Any prescription must therefore be accompanied by an explanation of the different steroid potencies Conventional potency gradings, as listed in the *British National Formulary*,[20] mean nothing to the layman, so an analogy with alcoholic drinks is helpful. There are four categories of topical steroid potency: grade IV, mildly potent, the 'shandy' of the range, grade III, moderately potent, 'sherry', grade II, potent, 'whisky'; grade I, highly potent, 'pure alcohol'.

In practice the major hazard of topical steroids is skin atrophy, resulting from regular use of the more potent preparations (categories III, II, and I), especially on the face. It is helpful for parents to know that this is virtually impossible to achieve with hydrocortisone. It is common to find circular areas of hypopigmentation in the region of eczematous lesions, especially after the child has been in the sun. Most parents wrongly assume that this is a side effect of the steroid and are helped by being told about the non-specific suppression of pigment production resulting from any localised skin disorder.

**2 Dry skin.** The skin is invariably dry in atopic eczema, so an ointment based steroid will be more effective than a cream. A potent cream-based preparation can usually be replaced with a weak steroid ointment. The regular use of an emollient—for example, emulsifying ointment—is likely to cut down dryness and may reduce the need for topical steroids The combination of a topical steroid with an antiseptic (such as clioquinol) may be useful where there has been a previous tendency to crusting, or weeping pustules which are signs of bacterial infection.[21]

**3 Knees, wrists, and ankles.** In older children it is common to see severe and heavily lichenified—that is, thickened—patches of eczema confined to the front of the knees, the wrists, and the ankles. Such lesions may not respond well to mildly potent steroids, and here it makes no sense to withhold a category II or III preparation because of fear of skin atrophy.

**4 Severe generalised lesions.** The larger the area of skin affected, and the more inflamed the skin, the greater is the risk of systemic absorption of a topical steroid. There is a theoretical risk of iatrogenic Cushing's syndrome with the widespread application of topical steroids, but the dearth of reported cases suggests that this is exceedingly rare. While atopic eczema is not a fatal condition, it is easy to forget how severe the resulting handicap and damage can be. To withhold mild or moderately potent steroids in such patients for fear of side effects is unreasonable. Indeed, in a few rare patients who are unresponsive even to the most stringent antigen avoidance regimens, life is only tolerable with the aid of regular systemic steroids.

Growth impairment is a feature of up to 10% of children with atopic eczema.[22] There is no evidence that the use of mild or moderately potent topical steroids contributes to this, although the long term use over large areas of skin of potent or very potent preparations, probably inhibits growth [22]

**5 Dilution.** Diluting proprietary preparations is misguided either the dilute result retains the potency of the original preparation, or the efficacy is changed in some uncontrolled way because mixing different vehicles may produce unpredictable changes in bioavailability. Certain substances—for example, salicylic acid or urea considerably enhance the skin penetration of steroids. It is better to decide on the potency required and use a proprietary preparation than opt for 'Dr X's ointment' (containing steroid, tar paste, and paraffin) the magic qualities of which are usually attributable to a highly potent steroid.

**6 Infection.** In theory topical steroids could exacerbate an area of infected eczema. In practice this does not occur,[23] and the problem is not mistreatment with steroids but failure to recognise and treat infection.[21] Topical steroids do not precipitate either initial or recurrent infections with herpes simplex.[24]

## Conclusions

The fear of side effects causes some doctors to withhold safe and effective treatment with steroids. Asthma and eczema can both be disabling and handicapping diseases, and in both, undertreatment is currently far more common than overtreatment. Untreated, both diseases can impair growth, and successful treatment usually reverses this

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# Monitoring oxygen in the newborn: saturation or partial pressure?

Pulse oximeters are a new type of medical equipment. They have been welcomed warmly into adult intensive care and anaesthetics, where there was little rival technology and no fear of arterial hyperoxia. In neonatal intensive care, though, where efficient monitoring of partial pressure is well established and too much oxygen is almost as worrying as too little, the place of oximetry is less clear The several oximeters now available are undeniably sophisticated instruments, but they are too expensive to be left gathering dust in the equipment cupboard because they failed to fulfil expectations. This article assesses what can and cannot be expected of oximetry in monitoring oxygen treatment in the newborn.

## How pulse oximeters work

Oximeters make use of the fact that oxyhaemoglo-in and deoxyhaemoglobin absorb light at the red end of the spectrum differently; deoxyhaemoglobin absorbs more red than infrared and oxyhaemoglobin more infrared than red. The oximeter probe consists of a light emitter and a light sensor, which are aligned on opposite sides of a narrow part of the body, such as the palm or forefoot in the case of a baby. The emitter sends equal intensities of red and infrared light into the tissue, and the sensor detects the ratio of red to infrared that emerges. From this information the proportion of oxyhaemoglobin to deoxyhaemoglobin—that is, the percentage saturation of haemoglobin with oxygen—is calculated and displayed. As the instrument measures a ratio rather than an absolute value no external calibration is necessary.

So that the oximeter measures the saturation of arterial blood rather than capillary or venous blood the instrument is programmed to look only at pulsatile increases in oxyhaemoglobin concentration—hence the term 'pulse' oximetry. For accurate measurements of arterial saturation a reasonable pulse must be detected Most available oximeters use a 'bouncing light' display to indicate the pulse amplitude and will give warning when the pulse is inadequate for reliable measurements At least one model displays an image of the pulse waveform, which allows the user to judge the signal quality

## Relation between saturation and partial pressure

Normally, 98% of the oxygen in arterial blood is bound to haemoglobin and 2% is dissolved in plasma. Oxygen electrodes, whether in a blood gas analyser, an arterial catheter, or a transcutaneous monitor, measure the partial pressure of dissolved oxygen. In the physiological range, however, the amount of oxygen taken up by haemoglobin is a function of the partial pressure of dissolved oxygen, so that a measurement of partial pressure provides an assessment of the oxygen content of haemoglobin. The precise relation is described by the haemoglobin/oxygen dissociation curve, in which the oxygen content of haemoglobin is usually expressed as a percentage of the maximum possible content—that is, percentage saturation The sigmoid shape of the curve, which is a key factor in any discussion of oximetry, is highly relevant to the function of haemoglobin. The flat section, which is principally concerned with oxygen uptake, ensures that arterial blood leaves the lung well saturated even when the partial pressure is reduced to about 9 kPa—say by modest lung disease or living at altitude. The steep lower portion ensures an adequate oxygen supply to tissues by releasing large amounts of oxygen for relatively small decreases in partial pressure.

There are several important influences on the relation between partial pressure and saturation. Those most relevant to neonatology are the change from fetal haemoglobin to adult haemoglobin, either naturally or due to transfusion, and changes in pH. Increasing concentrations of adult haemoglobin move the dissociation curve to the right, as does a fall in pH. Both of these effects are most pronounced on the steep portion of the curve. and I discuss their influence on tissue oxygenation and the interpretation of oxygen tension and saturation below.

Most paediatricians are familiar with partial pressure and find saturation less comprehensible. Developing a feel for the relation between the two is helped by a ready means of conversion Any programmable calculator can be used to convert saturation values to partial pressures and vice versa, making allowance for the type of haemoglobin and the pH. Hellegers *et al* give the formulae needed for these calculations[1]

### Tissue oxygenation

The supply of oxygen to the tissues does not depend solely on the oxygenation of haemoglobin because blood flow, haemoglobin concentration, and tissue oxygen consumption are also important. In so far as it does depend on haemoglobin oxygenation, however, the important factor is the amount of oxygen released by haemoglobin as the partial pressure of oxygen in arterial blood equilibrates with the partial pressure of oxygen in the tissue. This is determined by the difference in the saturation of haemoglobin at the two partial pressures and is a property of the slope of the dissociation curve rather than of either the absolute partial pressure of oxygen in plasma or the absolute percentage saturation of haemoglobin. For example, the reason that fetal haemoglobin suits the fetus is that, between the partial pressure of oxygen in fetal blood (about 4 kPa) and the partial pressure of oxygen in fetal tissue (about 2 kPA), the dissociation curve of fetal haemoglobin is steeper than that of adult haemoglobin. The fact that fetal haemoglobin is 'left shifted' compared with adult haemoglobin is important only in so far as it makes that dissociation curve steeper over the relevant range. The fact that fetal haemoglobin has a 'greater affinity for oxygen'—that is, a higher percentage saturation at a given partial pressure—is in itself irrelevant as far as tissue oxygenation is concerned; after all, carboxyhaemoglobin has a high affinity for oxygen. The purpose of this line of argument is to try to remove from the saturation/partial pressure debate the notion that either one alone is more relevant than the other to considerations of tissue oxygenation. Knowing both is quite a different matter.

### Interpreting measurements of partial pressure ($Pao_2$) and saturation ($Sao_2$)

Several published articles, including two in this issue,[2 3] have related oximeter readings to simultaneous measurements of partial pressure. They have all found a satisfactory overall correlation between the two, which describes the familiar shape of the oxygen dissociation curve of haemoglobin. A closer look, though, shows that over the upper section of the curve a wide range of partial pressure corresponds to a narrow range of saturation, and that over the lower portion of the curve the opposite is true. This effect is magnified in the published work because the graphs are constructed from pooled data from several babies; nevertheless, it is an inherent effect of the shape of the dissociation curve. These observations are relevant to the interpretation of saturation and partial pressure measurements and will be discussed in relation to higher and lower levels of arterial oxygenation.

AT HIGHER LEVELS OF OXYGENATION ($Pao_2 > 12$ kPa, $Sao_2 > 97\%$).

As long as oxidative insults to the developing retina are thought to contribute to the pathogenesis of the retinopathy of prematurity, excessively high partial pressures of oxygen in arterial blood during oxygen treatment must be avoided. There is no need to consider here exactly what constitutes 'excessive', but for the sake of argument let us say that the partial pressure should not be allowed to exceed 12 kPa. Given fetal haemoglobin and a normal pH, this corresponds to a saturation of about 97%, which is well on to the flat part of the dissociation curve. It is easy to show that even if the limits of accuracy of an oximeter were as good as ± 2% a partial pressure of 18 kPa is compatible with a saturation reading of 97%. If the oximeter sometimes underestimated the true saturation by as much as 5% it would be necessary to keep the reading below 92% in order to be sure of not exceeding a partial pressure of 12 kPa.

Clearly, oximetry alone cannot guard against hyperoxia on the upper reaches of the dissociation curve and, in the case of a preterm baby receiving oxygen, partial pressure should be monitored when the saturation is greater than 90%. Preterm babies with good lungs will of course exceed 90% saturation when breathing air, but in these circumstances concern about excessive partial pressures is rarely, if ever, relevant. In cases where hyperoxia is not a concern oximetry provides a satisfactory and reliable means of monitoring oxygen treatment and a saturation in the range of 90–95% should be ideal.

AT LOWER LEVELS OF OXYGENATION ($Pao_2$ 6–10 kPa, $Sao_2$ 85–95%).

During neonatal intensive care the partial pressure of oxygen is often maintained at levels that fall on the steep part of the dissociation curve. This is mainly influenced by the spectre of retinopathy, although sometimes lung function is too poor for arterial oxygenation to be improved beyond this point. But, even when it is possible to improve oxygenation, there may be an argument for not attempting to improve it much beyond the minimum required for tissue oxygenation as this usually means using a higher mean airway pressure, which probably increases the risk of barotrauma and chronic lung disease.

The steep part of the dissociation curve is a dangerous place, though, where quite small changes in oxygen tension produce large changes in saturation, and a change in pH has a much greater effect on saturation than it would on the upper reaches of the curve. For these reasons arterial oxygenation at lower levels is more sensitively monitored by an oximeter than by an oxygen electrode. As an example, take a change in arterial pH from 7·4 to 7·25 at a constant $Pa_{O_2}$ of 6 kPa The saturation will fall from about 88%, which is satisfactory. to about 80%, which may be too low for adequate tissue oxygenation at a $Pa_{O_2}$ of 6 kPa. An oximeter will detect this, a device measuring partial pressure will not.

As a guide saturations above 85% are satisfactory, between 85% and 80% may be satisfactory if the partial pressure is above 6 kPa, and below 80% are unsatisfactory: that is, assuming a normal cardiac output and haemoglobin concentration in each case.

Despite the benefits of monitoring saturation at lower levels of oxygenation partial pressure still cannot be ignored because it determines the rate and duration of oxygen transfer to the tissues and also the muscle tone in the wall of the ductus arteriosus and the pulmonary arterioles.[4] These effects cannot be exactly quantified, but the $Pa_{O_2}$ should probably be kept above 5 kPa whatever the saturation.

## Pulse oximetry in practice

The pulse oximeter is an easy instrument to use. It needs neither calibration nor a warm up period and so gives usable data from the moment it is fixed to the patient. The response time is fast, and the correlation between oximeter readings and direct measurements of saturation on arterial blood is good. The mean absolute difference between oximeter readings and direct measurements of saturation is in the region of 3%.[5] The display of heart rate could be an important feature if the oximeter is used during resuscitation in the labour ward, which might be a useful role for the instrument The probes supplied with the current oximeters are adequate rather than ideal, and could undoubtedly be improved with babies in mind. Compared to the problems of skin damage from transcutaneous electrodes, however, there is little to complain about.. Oximeters are upset by a lot of patient activity and will alarm frequently if the limits are not set wide in these circumstances. Reliable readings can be expected only during quiet periods. The state of peripheral perfusion seems less critical to oximeters than to transcutaneous monitors, and they are rather less influenced by oedema. Jaundice has a slight effect on oximeter readings, but too little to matter with modern instruments. The oximeter probe must be shielded from phototherapy lights or it will not function properly.

## Conclusion

It is tempting to regard oximeters mainly as rivals to transcutaneous oxygen monitors and to debate the relative merits of the two systems under similar circumstances. It is true that oximetry is useful for routine non-invasive monitoring of oxygen treatment on many occasions, but to limit its use to that purpose is to underestimate the potential value of measuring saturation in addition to partial pressure during intensive care, particularly at lower levels of oxygenation. Barriers to the acceptance of oximetry in neonatology should be easily overcome once it is seen as an additional means of monitoring rather than an alternative.

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## *Original articles*

# Pulse oximeter and transcutaneous arterial oxygen measurements in neonatal and paediatric intensive care

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SUMMARY Pulse oximeter ($SaO_2P$) measurements were compared with direct arterial line oxygen saturation ($SaO_2$) from co-oximeters in 92 instances in 43 patients, and with arterial line oxygen measurements ($PaO_2$) in 169 instances in 81 patients. The mean (SD) absolute difference between $SaO_2P$ and $SaO_2$ was 2·6% (2·4) after attempt to correct for the co-oximeter falsely measuring a proportion of fetal haemoglobin as carboxy haemoglobin. For 19 infants and children ≥5 months old, who have very little fetal haemoglobin, the mean (SD) absolute difference of 27 comparisons was 1·8% (2·1). Comparison of $SaO_2P$ and $PaO_2$ measurements in 46 instances when $PaO_2$ was <6·67 kPa showed $SaO_2$ to be <90% on 40 occasions. In 24 instances when $PaO_2$ was ≥13·3 kPa the $SaO_2P$ was ≥98% on 22 occasions. In 23 infants undergoing neonatal intensive care, transcutaneous oxygen monitors were compared with arterial $PO_2$ measurements in 60 instances. The mean (SD) absolute difference between $PaO_2$ and transcutaneous oxygen measurements was 1·60 kPa (1·73). Ten of the 60 comparisons had differences >2·67 kPa and three >5·33 kPa (maximum 8·40 kPa).

Pulse oximetry is a clinically useful technique for managing oxygenation but further studies are needed to confirm its safety in premature infants at risk of retinopathy of prematurity.

Information concerning the adequate uptake, transport, and unloading of oxygen is vital in the management of infants and children undergoing intensive care. While indwelling arterial lines can be used to obtain these data, insertion of catheters may be difficult and cause discomfort and serious side effects; thrombosis and blood loss may occur. Samples taken by stab give unreliable data and the procedure is painful Correction of the anaemia caused by repeated blood sampling is usually achieved by transfusion of adult haemoglobin. By changing the position of the oxygen dissociation curve, these transfusions may compromise uptake of oxygen in the lungs if there is a low alveolar $PO_2$. To overcome the problems inherent in repeated blood sampling heated transcutaneous $PO_2$ monitors ($TcPO_2$) have been widely adopted. Although overall correlations between $TcPO_2$ and arterial $PO_2$ ($PaO_2$) are high,[1–4] a considerable proportion of the comparisons reported have shown differences between transcutaneous and arterial line measurements This is particularly important when these monitors have been used for clinical rather than research purposes[2 5 6] Lack of agreement between $TcPO_2$ and $PaO_2$ measurements is particularly likely in infants older than 8 weeks[7] and when skin perfusion is poor.[8 9] To compensate for these errors it is the policy in some intensive care units, including ours, to validate $TcPO_2$ measurements using samples from arterial line.

In other units, however, $TcPO_2$ values are regarded as reliable enough to direct changes in inspired oxygen concentrations and mechanical ventilator management without such validation.

In this study we report our experience with pulse oximetry ($S_1O_2P$) and $TcPO_2$ measurements in the monitoring of oxygenation in neonatal and paediatric intensive care.

## Patients and methods

A total of 85 infants and children were studied. Twenty four were undergoing treatment in the neonatal intensive care unit at St Mary's Hospital. Their ages ranged from 1 to 47 days, gestational age at birth from 24 to 40 weeks, and birth weights from 690 to 3970 g. Most of them (99%) were receiving additional inspired oxygen, 70% were being ventilated, and 12% were receiving continuous positive airways pressure (CPAP).

The remaining 61 infants and children were undergoing treatment at the Brompton Hospital; 53 were receiving paediatric intensive care and eight undergoing cardiac catheterisation. Their ages ranged from 1 day to 13 years, 53 had congenital heart disease and eight had major respiratory disorders.

A pulse oximeter sensor (Nellcor) was used to obtain non-invasive measurements of arterial oxygen saturation In this technique[10 11] light of two wavelengths is transmitted through a tissue bed from the surface of the skin. On the opposite side of the tissue bed there is a photodetector which senses the transmitted light. Within the oximeter a light plethysmograph is constructed for each arterial pulse waveform in the tissue bed and calculations made of the light absorption with each pulse. Thus background colour change is ignored (except in terms of the intensity of the light source), and only pulsatile (arterial) light absorption measured. The technique is independent of skin colour, thickness, or texture. The response time is affected if the application site is cold, even if pulsations are present, and the instrument cannot work in the presence of very low arterial blood pressures. Audible alarms can be set for low saturation readings and for high or low heart rates. The amplitude of the light plethysmograph used to calculate each saturation value is displayed on the front of the machine as a linear array of diodes emitting light. The calculation of saturation by the oximeter was expressed as an average over a particular time period; an average of two to three seconds of data was taken in this study, during which time the arterial waveforms had to be of adequate quality—that is, resemble blood pressure waveforms and be of adequate amplitude compared with baseline noise. For most of our comparisons the analog output of each arterial waveform was examined on an oscilloscope.

The pulse oximeter sensor was attached to the child's finger, toe, or lateral side of the hand or foot in a position which matched the arterial line, thus avoiding possible errors caused by intracardiac or ductal shunts. The sensor was covered with a dark blue mitten or sock to reduce the effect of ambient light, particularly during phototherapy.

$PaO_2$ measurements from the arterial line samples were made on autocalibrating blood gas analysers (Corning 178 and Radiometer ABL) within two minutes of sampling. Calibrations were checked daily by chemical pathology technicians against standard reference solutions at three levels Samples of blood from arterial lines were analysed for oxygenated and reduced haemoglobin, carboxyhaemoglobin and methaemoglobin on co-oximeters (Corning 2500 or IL282), also within two minutes of sampling. These instruments were calibrated against control solutions once daily.

Pulse oximeter measurements were compared with arterial line $PO_2$ concentrations on 169 instances in 81 patients, and with arterial line saturation measurements corrected for methaemoglobin and carboxyhaemoglobin on 92 instances in 43 patients.

Measurements of $TcPO_2$ (Hewlett Packard 78850A, Radiometer TCM20, Kontron 820, and Novametrix 850) were made at skin temperatures of 44°C, and the sites for comparisons were chosen to avoid inconsistencies that could result from a right to left shunt. All $TcPO_2$ sensors were applied by trained nurses, and were recalibrated before each application (at four hourly intervals) for each patient. No infant was allowed to lie on the sensor. $TcPO_2$ monitors were used only in the neonatal intensive care unit

Measurements of $TcPO_2$ were compared with arterial line $PO_2$ measurements in 60 instances on 23 infants (mean age 10·5 days, maximum 47 days).

When comparing alternative methods of measurement, correlation coefficients may be of interest but in many cases are misleading, so they were not included. The absolute differences were analysed on the assumption that measurements from arterial line samples are more accurate than any other method.

The pulse oximeter measures oxyhaemoglobin as a proportion of the total functional haemoglobin present—that is, only oxygenated + reduced haemoglobin. Co-oximeters also measure methaemoglobin and carboxyhaemoglobin, and these must be taken into account when comparing pulse oximeter and arterial line sample measurements. With samples from infants younger than 5 months, a variable is the unknown amount of oxygenated fetal haemoglobin present Although this is a functional haemoglobin and is treated as such by the pulse oximeter, part of the fetal haemoglobin is falsely estimated as carboxyhaemoglobin by both co-oximeters. The proportions of fetal and adult haemoglobin, together with as yet undetermined factors, have been shown to affect the relation between this measured carboxyhaemoglobin and true carboxyhaemoglobin.[12 13] To overcome this problem comparisons of $SaO_2$ in this study have been shown separately for infants above and below 5 months of age. After 5 months, fetal haemoglobin concentrations will be low.[14]

For all measurements a correction formula described by Brown[15] and recommended by the manufacturers of the co-oximeters was used to provide values for functional $SaO_2$. This formula is: functional $SaO_2$ (%)=Fractional $SaO_2 \times 100/100-$(carboxyhaemoglobin+methaemoglobin); fractional $SaO_2$=oxygenated haemoglobin/(oxygenated haemoglobin+reduced haemoglobin+carboxyhaemoglobin+methaemoglobin).

## Results

Comparisons of $SaO_2P$ and arterial $SaO_2$ were made on 65 occasions in 24 infants less than 5 months old, and on 27 occasions in 19 infants and children over 5 months of age. Fig 1 shows the results of all comparisons, and fig 2 those for infants and children over 5 months of age. The variability between the two values, measured as the mean (SD) absolute difference for all patients, was 2·6% (2·4). Twelve of 92 comparisons (13%) showed differences ≥5% (maximum 10%). For 19 infants over 5 months old the mean (SD) absolute differences of 27 comparisons was 1·8% (2·1) and only four (15%) showed absolute differences ≥5% (maximum 7%).

The mean actual (signed) difference for infants under 5 months old was +2·08%, and for those over 5 months +0·74% (in both instances the mean for the co-oximeter exceeded the mean for the pulse oximeter).

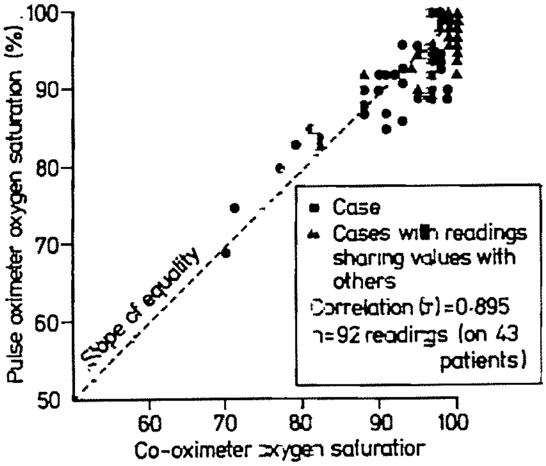

Fig. 1 *Comparison of $SaO_2$ from pulse oximeter with functional $SaO_2$ from arterial line blood samples measured by co-oximeter in all subjects*

Fig 3 shows the pulse oximeter values plotted against arterial line $PaO_2$ measurements made on 169 instances in 81 patients. Some of the variability shown in this figure may be due to a range of dissociation curves showing differing displacements to the left, typical in preterm babies with high concentrations of fetal haemoglobin. Comparisons of $SaO_2P$ and $PaO_2$ in 46 instances when $PaO_2$ was <6·67 kPa showed $SaO_2P$ <90% on 40 occasions,

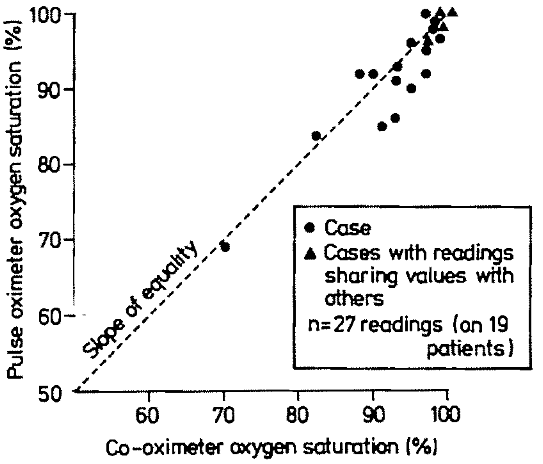

Fig. 2 *Comparison of $SaO_2$ from pulse oximeter with functional $SaO_2$ from arterial line blood samples measured by co-oximeter in subjects over 5 months.*

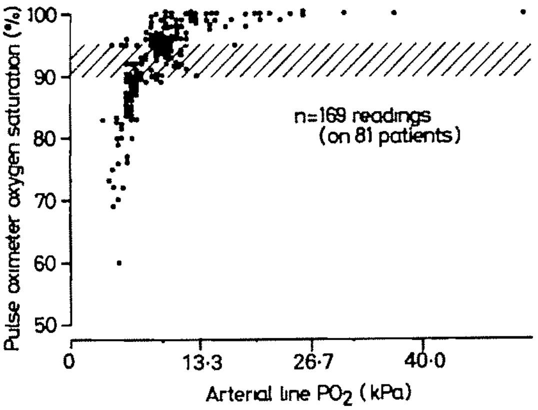

Fig 3 *Comparison of $SaO_2$ from pulse oximeter with $PO_2$ from arterial line blood samples*

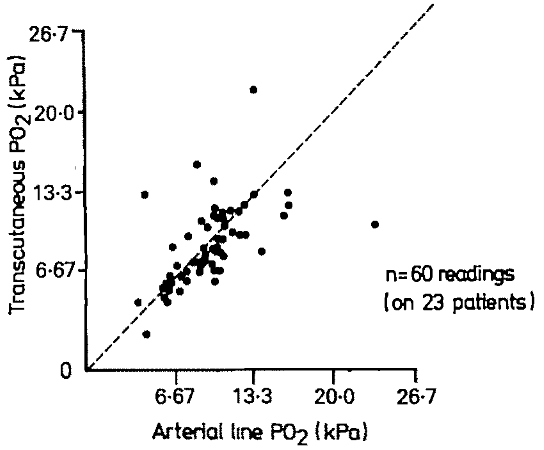

Fig. 4 *Comparison of transcutaneous PO$_2$ with PO$_2$ from arterial line blood samples*

while in 24 instances when PaO$_2$ was $\geq$13·3 kPa the SaO$_2$P was $\geq$98% on 22 occasions.

TcPO$_2$ and arterial line PaO$_2$ were compared on 60 instances in 23 infants (fig 4). The mean (SD) of the absolute differences between TcPO$_2$ and PaO$_2$ was 1·67 kPa (1·73). Ten of the 60 comparisons (on six different infants and four different machines) showed differences of >2·67 kPa. Three comparisons on three different infants showed differences >5·33 kPa (maximum 8·40 kPa).

## Discussion

When care is taken to use only high quality arterial waveforms, pulse oximetry is a useful, non-invasive technique and represents a considerable advance in monitoring oxygenation in infants and children undergoing intensive care. Our experience is similar to that of others,[2] [16–20] but this study has highlighted the problem of measuring fetal oxygenated haemoglobin saturation in infants under 5 months old when validation of SaO$_2$P is seriously limited by the inaccuracy of the co-oximeters. After an empirical correction for the false measurement of a proportion of oxygenated fetal haemoglobin as carboxyheamoglobin, the mean absolute difference between SaO$_2$P and SaO$_2$ was 2·6%. When comparisons were limited to an age at which fetal haemoglobin concentrations were low, the mean absolute difference was 1·8% and exceeded 4% in four of 27 comparisons.

Recently corrections according to the proportions of fetal haemoglobin have been published by Cornelissen *et al*[13] and Ryan *et al*[12] Nevertheless, we suggest that in future studies the base line measurement would be better obtained by using a non-spectrophotometric method of measuring arterial blood sample oxygen saturation—for example, from direct measurement of oxygen content.

Over the steep part of the dissociation curve, the most important part of the reading in ill patients with problems associated with tissue oxygenation or the uptake of oxygen from the lungs, the quantity of oxygen transported in the blood, and the availability of oxygen are more usefully reflected by oxygen saturation than by PaO$_2$. In the presence of fetal haemoglobin where the curve is shifted to the left, SaO$_2$ may be adequate at relatively low values of PaO$_2$, and increasing the PO$_2$ may not increase the unloading of oxygen to the tissues. With fetal haemoglobin present oxygen saturation may be 95% at a PaO$_2$ of 6·67 kPa. When the curve is shifted to the right, as in acidosis, with increasing temperature, or following transfusion of adult blood, optimal availability of oxygen to tissues may require relatively higher PaO$_2$ values. Under these circumstances a PaO$_2$ of 12·7 kPa may be required to provide 95% saturation, the saturation being only 70% at a PaO$_2$ of 6·67 kPa.

As far as clinically important hypoxaemia is concerned, analysis of our data shows that in 46 instances with a PaO$_2$ <6·67 kPa, oxygen saturation was <90% on 40 occasions. Figure 3 shows that the steep part of the curve begins at about 90% We suggest that values less than this should be avoided.

The problem of avoiding hyperoxaemia when using SaO$_2$ rather than PaO$_2$ measurements is of major concern in neonatal intensive care because of the risk of retinopathy of prematurity[21] [22]; a large and possibly harmful change in PO$_2$ can occur in the presence of small or, in the case of 100%, zero change in saturation values. In this respect, TcPO$_2$ could provide a more reliable indicator of hyperoxaemia. In practice, however, the reliability of TcPO$_2$ measurement decreases as PaO$_2$ increases.[1] [2] [5] [6] It was reassuring to note that using pulse oximetry in the 24 instances when PaO$_2$ was $\geq$100 mmHg, the SaO$_2$P was $\geq$98% on 22 occasions. Nevertheless, in the presence of additional inspired oxygen or CPAP, our data suggest that to avoid PaO$_2$ values of >13·2 kPa in newborn preterm infants true arterial oxygen saturation values of >95% should be avoided. In our data from patients over 5 months of age the co-oximeter exceeded the pulse oximeter by 2% or less in 85% of instances with a maximum of 7%. This relatively small quantity of information from older infants does suggest that pulse oximeter values of 90% should avoid hyperoxia. Nevertheless, more investigations into the calibration and validation of pulse oximeters for use in neonates are required. Without additional inspired oxygen, SaO$_2$P values in healthy normal infants are often >98%, and this safety level of 91% is only relevant when additional oxygen is being given.

In practice it is vital that the operator appreciates the number of arterial pulse waveforms (or the time) over which the pulse oximeter is averaging saturation. Measurements of saturation averaged from over a long time period should theoretically decrease errors and damper any short term oscillations in saturation. Long term average measurements will, however, provide accurate readings only if all of the waveforms are of adequate quality. Measurements made more often over short average times should avoid this possible source of error, and are probably a safer way of using this instrument. It is essential that the quality of all waveforms used to derive a particular saturation value are adequate. Fig 5 shows the kind of artefact that may result from inadequate waveforms. The monitor used in this present study provided a bouncing light display to indicate the quality of each waveform; we consider that this may be insufficient. A monitoring oscilloscope showing the quality of the waveforms on which the calculations were based would be useful. Alternatively, the analog output of the arterial waveform signals could be displayed on ECG monitor at the bedside.

Previous investigators[1-9] have examined correlations between TcPO$_2$ and arterial line PO$_2$ measurements, and the lack of reliable comparisons by clinicians as distinct from research workers has been well documented.[2 5 6] Fanconi *et al*[2] reported a mean absolute difference of 0·93 kPa (range −1·87 to +5·53), with 10 of 108 values differing by >2·67 kPa, and Kraus *et al* reported that about 20% of values differed by more than 2·67 kPa.[6] Similarly our data (fig 4) shows that 10 of 60 comparisons differed by more than 2·67 kPa, and three of 60 by >5·33 kPa, (maximum 8·40 kPa). Inexplicable and clinically relevant differences between TcPO$_2$ and PaO$_2$ measurements have been identified,[3] and our study confirms that TcPO$_2$ measurements must be validated frequently, and that changes in inspired oxygen must not be based on TcPO$_2$ alone but always checked by blood gas analysis.

TcPO$_2$ measurements are known to become less reliable as patients get older,[7] and they are unsuitable for older preterm infants with chronic lung disease who are receiving additional inspired oxygen. Pulse oximetry may be particularly valuable in this group.

Potential advantages of the pulse oximeter include the rapidity of achieving a measurement after the probe has been applied, the internal calibration, the lack of skin heating, and the fact that the characteristics of the arterial waveforms indicate whether the probe has been correctly applied. This last advantage is particularly important; TcPO$_2$ electrodes do not have this capacity.

The major disadvantage of the pulse oximeter is its susceptibility to artefacts caused by movement. This is probably inherent in the 'transmission' method and may be difficult to overcome. While the babies were crying, squirming, or having seizures, when SaO$_2$ may well fall, the monitor was unable to identify satisfactory arterial waveforms for the measurement of saturation. Fig 6 illustrates short lived episodes of true arterial hypoxaemia during short apnoeic pauses and periodic breathing in normal preterm and fullterm infants, which may

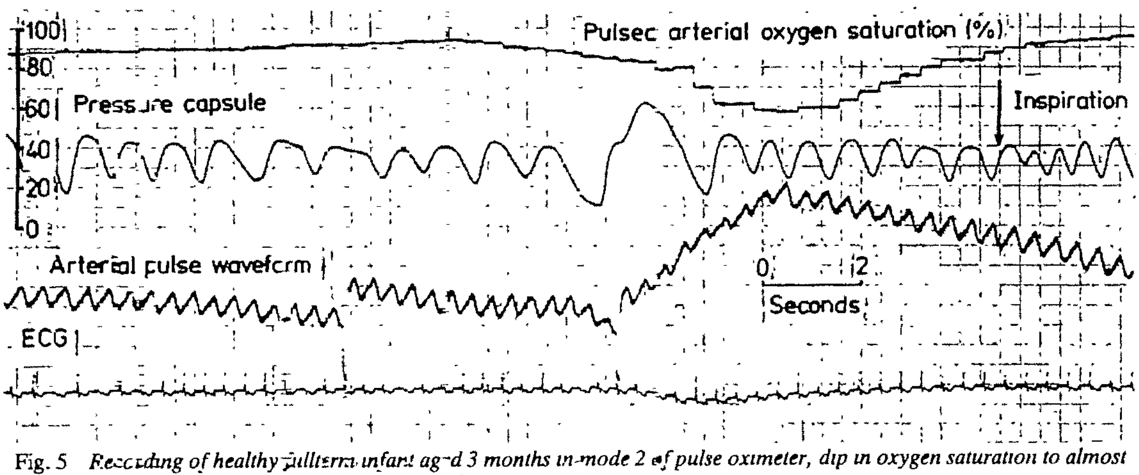

Fig. 5 *Recording of healthy fullterm infant aged 3 months in mode 2 of pulse oximeter, dip in oxygen saturation to almost 60% without an apnoeic pause is due to artefact*

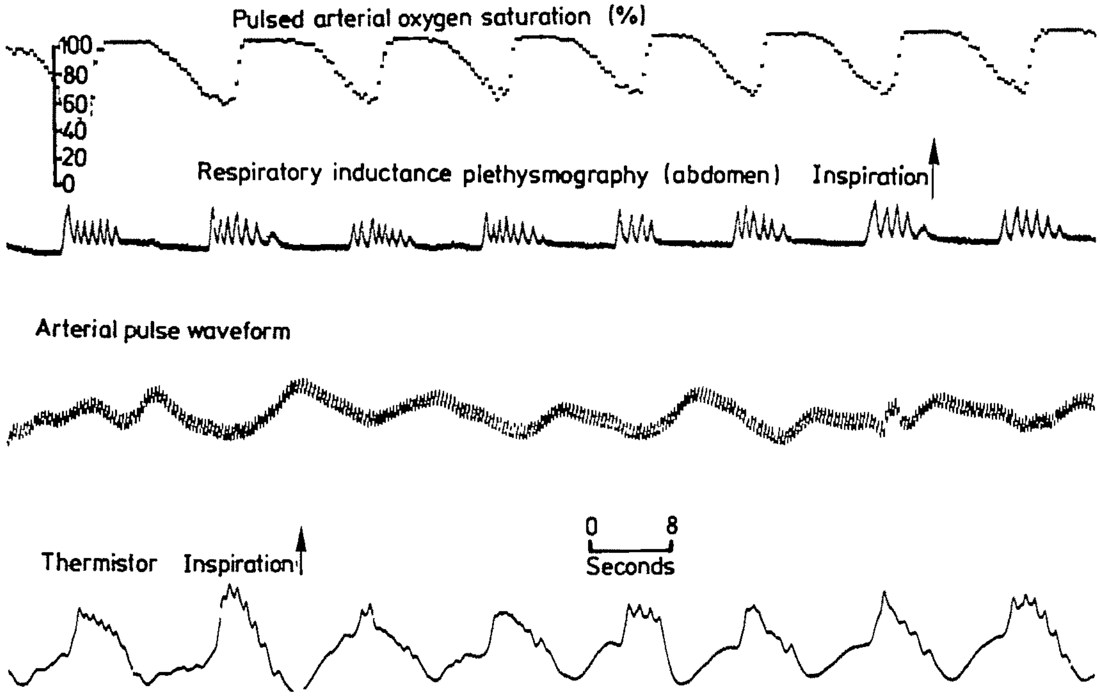

Fig 6 *Periodic breathing in apparently healthy preterm infant with dips in $SaO_2$ signal to around 60% after each apnoeic pause*

produce many low saturation alarms. To overcome this problem it would be necessary to be able to measure the duration of the hypoxaemia, or track a breathing movement signal, so that episodes of hypoxaemia associated with short apnoeic pauses and periodic breathing could be differentiated from persistent baseline hypoxaemia, or from hypoxaemia associated with prolonged apnoea. Other problems include the difficulty of being sure that the arterial waveforms are adequate and the relatively high cost of the probe; this may tempt nursing staff to use them on more than one patient, so increasing the risk of cross infection.

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# Bone mineral content in bronchopulmonary dysplasia

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SUMMARY Fourteen preterm infants who developed bronchopulmonary dysplasia diagnosed radiologically were compared with a group of similar infants who did not. The two groups were of comparable maturity and birth weight. The clinical histories indicated that those infants with bronchopulmonary dysplasia had had longer periods of supplemental oxygen, more frequent treatment with dexamethasone, and a higher mean total dosage of frusemide.

Bone mineral content in the mid-forearm was measured by photon absorptiometry at or near the postconceptional age of 40 weeks in all cases; no significant difference was found between the two groups, although both were severely undermineralised when compared with infants born at full term. In both groups mean daily calcium intake (about 70 mg/kg/day) was about half the daily intrauterine accretion of calcium.

Impaired skeletal mineral absorption is common in preterm infants after prolonged intensive care.[1] In such cases the deficit in bone mineral content (BMC) can be measured accurately by photon absorptiometry,[2] and we have shown that at a postconceptional age of 40 weeks the deficit in BMC in the mid-forearm compared with that in the arms of full term infants measured at birth is about 20%.[3 4]

Inability in postnatal life to match intrauterine skeletal mineral absorption may be exacerbated by several factors including prolonged intravenous nutrition with its inherent limitation on mineral intake[5]; fluid restriction, resulting in decreased intake of calcium and phosphorus; physiological losses of calcium and phosphorus in stool and urine, which limit the quantities retained; chronic acidosis[6]; and treatment with steroids[7] and diuretics.[8] These factors are more common in infants undergoing prolonged intensive care, who often develop bronchopulmonary dysplasia (BPD).

Although there have been reports of radiologically diagnosed bone disease occurring in conjunction with chronic neonatal lung disease,[9 10] only once to our knowledge has its severity been measured by photon absorptiometry.[11] As part of a larger study of bone mineral absoption in neonates we compared otherwise similar groups of preterm infants with and without BPD to ascertain whether undermineralisation was more severe in those with BPD.

## Patients and methods

This retrospective study was confined to infants who had undergone photon absorptiometry of the forearm at or near the postconceptional age of 40 weeks. Informed consent was obtained from the parents and the study approved by the hospital ethical committee.

Over a period of 26 months 14 infants who needed ventilation for hyaline membrane disease developed radiological and clinical evidence of BPD. Using established criteria,[12] a paediatric radiologist (RA) graded their chest radiographs as showing either moderate or severe BPD. Fourteen infants of similar maturity and birth weight who were in the unit during the same period were identified and formed the control group; they were selected because they too had been ventilated but their chest radiographs showed either mild or no changes of BPD. Table 1 shows the sex, gestational age, birth weight, and duration of stay in the unit of each infant.

The number of days of ventilation and the number of days of supplemental oxygen were recorded for each infant. Table 2 gives these details together with the number of days of intravenous fluid replacement, acidosis (blood pH less than 7·30, usually respiratory in origin), and treatment with dexamethasone (0·1 mg/kg/dose) when these data were available. Only one infant in the control group

Table 1 *Clinical details of infants studied*

| *Case No* | *Sex* | *Gestational age (weeks)* | *Birth weight (g)* | *Stay in unit (days)* |
|---|---|---|---|---|
| | | **Group with BPD** | | |
| 1 | F | 26 | 725 | 94 |
| 2 | F | 26 | 950 | 98 |
| 3 | M | 26 | 1010 | 84 |
| 4 | M | 26 | 1020 | 78 |
| 5 | F | 27 | 780 | 72 |
| 6 | F | 27 | 1125 | 91 |
| 7 | M | 27 | 740 | 70 |
| 8 | M | 27 | 1300 | 77 |
| 9 | M | 28 | 1000 | 60 |
| 10 | M | 28 | 1000 | 55 |
| 11 | F | 29 | 1200 | 98 |
| 12 | M | 29 | 1550 | 105 |
| 13 | M | 30 | 1300 | 82 |
| 14 | M | 30 | 1770 | 70 |
| Mean | | 27·57 | 1105 | 81·0 |
| SD | | 1·45 | 300 | 14·9 |
| SE | | 0·39 | 80 | 4·0 |
| | | **Control group** | | |
| 15 | F | 26 | 840 | 80 |
| 16 | M | 26 | 900 | 70 |
| 17 | M | 27 | 725 | 65 |
| 18 | M | 27 | 1000 | 91 |
| 19 | F | 28 | 1150 | 32 |
| 20 | F | 28 | 1500 | 84 |
| 21 | M | 28 | 1250 | 84 |
| 22 | M | 28 | 1300 | 63 |
| 23 | M | 28 | 1350 | 64 |
| 24 | M | 28 | 1450 | 38 |
| 25 | F | 29 | 1400 | 77 |
| 26 | F | 30 | 800 | 54 |
| 27 | F | 31 | 1100 | 52 |
| 28 | M | 31 | 1400 | 51 |
| Mean | | 28·21 | 1155 | 64·6 |
| SD | | 1·58 | 263 | 17·8 |
| SE | | 0·42 | 70 | 4·7 |

received dexamethasone (for laryngeal oedema). Table 3 shows the number of doses of frusemide (1–2 mg/kg) given to each infant; treatment with dexamethasone or frusemide, or both, was always stopped before discharge from the unit.

Oral fluid intake was used to derive energy and mineral intakes from manufacturers' data sheets. Table 3 lists the total calcium intake with corresponding mean daily intakes of fluid, energy, and calcium up to the day when photon absorptiometry was performed. Fluid intake was unknown in two cases.

We always supplement the milk with vitamin D (400 or 1000 IU daily) once oral feeds can be tolerated and vitamin D intake is usually recorded throughout each infant's stay in the unit; the mean daily intake over the period up to discharge was calculated for each infant and is also shown in table 3. No attempt was made to estimate vitamin D intake after discharge from the unit. Data were not available in three cases.

BMC in the mid-forearm was measured as previously described.[2 4] Photon absorptiometry of the forearm in neonates entails a small skin entrance dose of 0·03 mGy (3 mrads) for each investigation; a 0·5 cm length of forearm is irradiated. The procedure was done in 24 of the infants at postconceptional ages ranging from 37 to 41 weeks, and the remaining four within six days of these limits. Results are expressed as mass of ash per unit length (mg/cm). Crown-heel length (cm), weight (g), and ulnar length (mm) were measured when photon absorptiometry was performed. Table 4 shows the results of the radiological grading for evidence of BPD, the results of photon absorptiometry, and anthropometric data. Blood samples were taken for assay of plasma concentrations of 25-hydroxyvitamin D from 18 of the 28 infants on the day that absorptiometry was performed.[13] These results are also shown in table 4.

When the data were normally distributed the mean, standard deviation (SD), and standard error (SE) of each measurement were computed for each group and the significance of the difference between the two group means calculated with the unpaired Student's *t* test. Otherwise only the means were calculated and a non-parametric test (Mann-Whitney U test or Wilcoxon rank sum test) used to calculate the significance of the differences between the two groups. Two tailed probabilities are quoted throughout.

## Results

There were no significant differences in mean gestational age or birth weight between the infants with BPD and the controls (Table 1). Those with BPD spent significantly more time in the unit ($p < 0·02$; table 1) and required more days of ventilation ($p < 0·001$) and supplemental oxygen ($p < 0·001$, table 2) than the controls. Intravenous fluid replacement was undertaken significantly more often ($p < 0·01$) and acidosis occurred more frequently ($p < 0·005$) in the group with BPD than in the control group. Infants with BPD were treated more frequently with dexamethasone ($p < 0·005$; table 2); the mean total frusemide dosage was also significantly higher ($p < 0·05$; table 3).

The mean total calcium intake was significantly lower in the group with BPD than in the control group (6·46 g *v* 10·33 g; $p < 0·05$; table 3). The mean daily calcium intake in the group with BPD

Table 2 *Number of days of ventilation, supplementary oxygen, intravenous fluid replacement, acidosis, and treatment with dexamethasone therapy*

| *Case No* | *Ventilation* | *Oxygen* | *Fluids* | *Acidosis* | *Dexamethasone* |
|---|---|---|---|---|---|
| | | | **Group with BFD** | | |
| 1 | 32 | 84 | 45 | 22 | 24 |
| 2 | 23 | 65 | 30 | 29 | 30 |
| 3 | 49 | 98 | 38 | 37 | 9 |
| 4 | 20 | 56 | 19 | 15 | 11 |
| 5 | 17 | 28 | 34 | 15 | 9 |
| 6 | 24 | 27 | 32 | 13 | 0 |
| 7 | 26 | 88 | 42 | 18 | 0 |
| 8 | 12 | 22 | 41 | 8 | 22 |
| 9 | 31 | 20 | — | — | — |
| 10 | 22 | 85 | 40 | 30 | 8 |
| 11 | 21 | 26 | 24 | 10 | 31 |
| 12 | 37 | 36 | 38 | 14 | 0 |
| 13 | 18 | 36 | 29 | 14 | 38 |
| 14 | 37 | 69 | 44 | 14 | 7 |
| Mean | 26·4 | 52·9 | 35·1 | 18·4 | 14·5 |
| | | | **Control group** | | |
| 15 | 22 | 29 | 43 | 15 | 0 |
| 16 | 5 | 27 | 7 | 7 | 0 |
| 17 | 1 | 1 | 3 | 4 | 0 |
| 18 | 18 | 43 | 32 | — | 6 |
| 19 | 4 | 5 | 6 | 3 | 0 |
| 20 | 26 | 21 | 33 | 22 | 0 |
| 21 | 22 | 26 | 61 | 12 | 0 |
| 22 | 8 | 9 | 14 | 8 | 0 |
| 23 | 14 | 16 | 17 | 5 | 0 |
| 24 | 7 | 10 | 9 | 5 | — |
| 25 | 7 | 19 | 9 | 9 | 0 |
| 26 | 1 | 1 | 2 | 1 | 0 |
| 27 | 7 | 7 | 9 | 7 | 0 |
| 28 | 14 | 17 | 17 | 6 | 0 |
| Mean | 11·1 | 16·5 | 18·7 | 8·0 | 0·5 |

(expressed as mmol/kg/day) was also lower but not significantly so. Daily fluid and energy intakes were significantly lower in the group with BPD than in the control group ($p < 0·02$ and $p < 0·05$, respectively).

The group with BPD had a lower mean vitamin D intake than the control group (306 *v* 472 IU daily); this difference was significant ($p < 0·05$). The mean plasma 25-hydroxyvitamin D concentrations around the postconceptional age of 40 weeks were comparable and not significantly different between the two groups; in the group with BPD one infant had a value below 25 nmol/l whereas four controls had values below that limit.

At about 40 weeks the infants with BPD were on average lighter than the controls (table 4); the difference (about 430 g) between the group means was significant ($p < 0·05$). There were no significant differences between the two groups in mean crown-heel length, ulnar length, or BMC. Even when the extreme cases were contrasted the mean BMC did not differ significantly between those with and without BPD; mean (SE) BMC in nine infants classified as having severe radiological changes associated with BPD was 98·0 (5·5) mg/cm, and in 10 controls with no radiological evidence of BPD the corresponding value was 105·1 (11·4) mg/cm Although significant differences between groups could not be shown, the mean BMC was only about 100 mg/cm in both the BPD and control groups; in contrast, the mean value in full term infants measured at birth with the same apparatus has been shown to be 194·0 (3·7) mg/cm.[4]

## Discussion

During pregnancy the placenta provides the fetus with a readily available source of calcium and phosphorus. It has been estimated that the accretion of calcium in utero is about 130 mg/kg/day during

Table 3 *Total number of doses of frusemide and intake of calcium and average daily intake of fluid, energy, calcium, and vitamin D*

| *Case No* | *Total intake* | | *Daily intake* | | | |
|---|---|---|---|---|---|---|
| | *Frusemide (No of doses)* | *Calcium (g)* | *Fluid (ml/kg)* | *Energy (kJ/kg)* | *Calcium (mmol/kg)* | *Vitamin D (IU)* |
| | | | **Group with BPD** | | | |
| 1 | 22 | 5 72 | 172 | | 1 17 | 252 |
| 2 | 8 | 5 34 | 152 | 26 0 | 2 62 | 230 |
| 3 | 109 | 9·55 | 160 | 22 9 | 1 92 | 176 |
| 4 | 29 | | 137 | | | 853 |
| 5 | 7 | 3 65 | 157 | 20 3 | 1 14 | 453 |
| 6 | 7 | 3 86 | 149 | 17·7 | 1 15 | 582 |
| 7 | 50 | 7·49 | 140 | 20 6 | 1·50 | 213 |
| 8 | 0 | 8 96 | 138 | 19 0 | 1 71 | 220 |
| 9 | | 8 60 | 132 | 19 9 | 1 86 | |
| 10 | 60 | 4 44 | 137 | | 2 34 | 195 |
| 11 | 2 | | | | | |
| 12 | 49 | 12·93 | 135 | 9 9 | 1 81 | 143 |
| 13 | 0 | 1 38 | 133 | 5 5 | 0 99 | 281 |
| 14 | 114 | 5·60 | 134 | 7·7 | 1 40 | 77 |
| Mean | 35 2 | 6 46 | 144·3 | 20 0 | 1 63 | 306 |
| SD | | | 12·6 | 2 9 | 0 51 | |
| SE | | | 3·5 | 0 9 | 0 15 | |
| | | | **Control group** | | | |
| 15 | 11 | 14 45 | 143 | 23 7 | 1 81 | 475 |
| 16 | 1 | 13·92 | 165 | 26 0 | 2·14 | 478 |
| 17 | 0 | 7 63 | 219 | 33 7 | 3 16 | 384 |
| 18 | | 9·23 | 157 | 19 6 | 1 78 | 618 |
| 19 | 0 | 7 24 | 167 | 27 5 | 1 26 | 911 |
| 20 | 28 | 9 31 | 165 | 21 8 | 1 75 | 552 |
| 21 | 4 | 3 42 | 140 | 14·1 | 0 79 | 97 |
| 22 | 0 | 13 33 | 167 | 29·9 | 2 10 | 374 |
| 23 | 6 | 11 86 | 139 | 20 5 | 1 88 | 490 |
| 24 | 21 | 11 96 | 139 | 22 4 | 1·90 | 424 |
| 25 | 9 | | | | | |
| 26 | 0 | 15 48 | 187 | 31 3 | 2 66 | 464 |
| 27 | 3 | 6 11 | 165 | 26 4 | 1 41 | 592 |
| 28 | 6 | 10 35 | 153 | 22 4 | 1 77 | 273 |
| Mean | 6 8 | 10·33 | 162·0 | 24 6 | 1 88 | 472 |
| SD | | | 22·3 | 5 3 | 0 59 | |
| SE | | | 6 2 | 1 5 | 0 16 | |

the last trimester of pregnancy, resulting in the deposition of about 25 g of calcium in the fetal skeleton.[4] Because many premature infants have nutritional problems it is not surprising that inadequate skeletal mineral absorption is common. Although skeletal changes associated with neonatal bone disease can sometimes be detected radiologically,[5] the more sensitive technique of photon absorptiometry has shown that the bones of almost all premature infants are deficient in minerals by the time they reach the postconceptional age of 40 weeks.[3 4]

There are compelling theoretical reasons for believing that inadequate skeletal mineralisation should be more pronounced in infants who develop BPD. As we have shown, these infants are generally more ill and require longer periods of ventilation and supplemental oxygen with restriction of fluids, and hence lower calcium and phosphorus intakes. Although we did not attempt to carry out balance studies, in both the BPD and control groups the average daily calcium intake over the study period was far less than would be expected in utero Furthermore, the calcium available for absorption into bone was considerably less than the intake because retention was probably no more than 50%.[6] Calcium retention in the group with BPD was probably further reduced by treatment with

Table 4 *Observations at postconceptional age of 40 weeks*

| *Case No* | *Radiological grade** | *Weight (g)* | *Crown-heel length (cm)* | *Ulnar length (mm)* | *BMC (mg/cm)* | *25-Hydroxy vitamin D (nmol/l)* |
|---|---|---|---|---|---|---|
| | | | **Group with BPD** | | | |
| 1 | 3 | 1775 | 40·2 | 57·5 | 94·1 | |
| 2 | 3 | 2170 | 44·3 | 64·0 | 86·3 | |
| 3 | 3 | 1980 | 40·6 | 67·0 | 121·4 | 198 |
| 4 | 2 | 2700 | 44·5 | 69·0 | 92·0 | 149 |
| 5 | 3 | 2570 | 45·5 | 73·0 | 66·0 | |
| 6 | 3 | 1400 | 40·2 | 61·0 | 111·8 | 58 |
| 7 | 3 | 1620 | 39·5 | 61·0 | 89·2 | |
| 8 | 2 | 1990 | 43·5 | 69·0 | 101·1 | 113 |
| 9 | 3 | 1900 | 40·9 | 66·0 | 102·3 | |
| 10 | 3 | 1400 | 39·1 | 56·3 | 109·2 | |
| 11 | 2 | 1650 | 42·1 | 63·0 | 96·7 | 69 |
| 12 | 2 | 2650 | 46·9 | 73·0 | 129·7 | 8 |
| 13 | 2 | 1830 | 42·3 | 67·0 | 97·0 | 52 |
| 14 | 3 | 1450 | 43·8 | 60·0 | 101·3 | 25 |
| Mean | | 1935 | 42·39 | 64·77 | 99·86 | 84 |
| SD | | 446 | 2·41 | 5·28 | 15·57 | |
| SE | | 119 | 0·64 | 1·41 | 4·16 | |
| | | | **Control group** | | | |
| 15 | 0 | 2520 | 46·0 | 72·5 | 79·6 | |
| 16 | 0 | 3000 | 41·5 | 67·0 | 126·1 | 82 |
| 17 | 0 | 1600 | 40·0 | 58·0 | 65·0 | 4 |
| 18 | 1 | 1840 | 40·5 | 60·5 | 90·4 | |
| 19 | 0 | 2730 | 45·1 | 75·0 | 100·2 | 107 |
| 20 | 1 | 1650 | 40·2 | 64·0 | 87·5 | 23 |
| 21 | 1 | 1520 | 40·0 | 62·0 | 79·3 | 18 |
| 22 | 1 | 2500 | 45·0 | 69·0 | 104·7 | 15 |
| 23 | 0 | 2800 | 47·5 | 74·0 | 127·5 | 201 |
| 24 | 0 | 3450 | 50·8 | 85·0 | 124·0 | |
| 25 | 0 | 2180 | 44·6 | 69·0 | 93·2 | 78 |
| 26 | 0 | 2700 | 45·7 | 72·5 | 68·7 | |
| 27 | 0 | 1800 | 42·0 | 65·0 | 82·9 | 105 |
| 28 | 0 | 2780 | 48·2 | 75·0 | 183·5 | 131 |
| Mean | | 2362 | 44·08 | 69·18 | 100·90 | 76 |
| SD | | 599 | 3·45 | 7·15 | 31·17 | |
| SE | | 160 | 0·92 | 1·91 | 8·33 | |

*0 = normal, 1 = mild, 2 = moderate, 3 = severe BPD

frusemide, which is known to increase urinary calcium excretions.[8] Additionally, because steroids cause a reduction in the mineral content of bone in adults, it might be expected that treatment with dexamethasone would also have deleterious effects on the infant skeleton.[7]

Despite these expectations we did not detect a difference in BMC of the forearm between the BPD and control groups using the most sensitive technique available When compared with full term infants at birth the preterm infants with BPD observed at 40 weeks were severely deficient in minerals, but this seems to be a consequence of their prematurity and not a secondary effect of treatment. Greer and McCormick reached a similar conclusion, even though their controls were on average more mature and heavier than our infants with BPD.[11]

Though inadequate intake of both calcium and phosphorus is likely to be a major cause of mineral deficiency in preterm infants,[17] vitamin D deficiency is also associated with bone disease.[18] Although the babies in our study ultimately received the recommended intake of 400 IU/day, this could not be achieved until oral feeds were tolerated in sufficient quantities. Some infants received more vitamin D than is recommended (Table 3), and in some cases when enteral feeding was delayed the daily average intake over the period of stay in the neonatal unit was well below the recommended value. Although plasma 25-hydroxyvitamin D concentrations were similar in the two groups at the time that BMC was measured, when vitamin D intake was most likely to be optimal, those concentrations might not reflect earlier vitamin D state. Several infants had 25-hydroxyvitamin D values below the concentration regarded as indicating vitamin D deficiency (25 nmol/l) Within this set of data, however, no significant association between the plasma 25-hydroxyvitamin D concentrations and BMC could be shown.

The results of this study indicate that the skeleton is deficient in minerals in infants with BPD as a consequence of their prematurity. That such infants were not found to be more severely undermineralised than preterm controls without BPD was surprising. Both mineral and vitamin D intakes in preterm infants may be suboptimal during their stay in the neonatal unit, and both factors probably contribute to the development of neonatal bone disease, although the grossly deficient mineral intake (compared with the intrauterine accretion) may be the more important.[17] It is reassuring to know that the current treatment of BPD with frusemide and dexamethasone does not seem to be detrimental.[19]

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# Validity of forced expiratory flow volume loops in neonates

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SUMMARY It is claimed that suddenly squeezing a newborn baby's trunk with a pressure of 3–4 kPa produces a flow volume curve that can be used to measure the function of the small airways. If the squeeze is applied during expiration rather than at the end of inspiration, however, anomalous results may be obtained. One possible explanation is that the babies are limiting expiratory flow by making inspiratory efforts in response to the applied external pressure.

The response of 10 healthy term neonates to forced expiration was studied by using an oesophageal balloon. The squeeze was provided by an inflatable jacket, and measurements of oesophageal pressure and jacket pressure were recorded, as well as flow and volume changes at the mouth. Two hundred and twenty one squeezes were performed at different points in the respiratory cycle. In 188 squeezes an inspiratory effort was evident before the oesophageal pressure reached a plateau (mean time to peak pressure = 155 ms). For the remaining squeezes a plateau pressure was associated with closure or narrowing of the upper airway in most of the babies. When the squeeze was applied at low lung volumes the inspiratory effort was significantly earlier and stronger than around end inspiration. Thus a baby makes a reflex inspiratory response to chest compression that may interfere with the measurement of airway function when this technique is used.

Much of our knowledge of lung function is based on the results of tests on forced expiration. The peak flow is the simplest and most commonly used test, but more information can be obtained from a maximum expiratory flow volume curve. In particular, the shape of the curve for lungs with small volumes is altered by changes in the small airways. Flow rates in this part of the curve are independent of effort, and this limitation of flow is a function of the intrinsic mechanical properties of the lungs. As the technique requires the active cooperation of the patient it cannot be used in neonates or young children. A simple, reliable test of lung function in the first three years of life would have obvious benefits in assessing severity and progression of disease and in monitoring effects of treatment.

In 1977 Adler and Wohl described a method for obtaining partial forced expiratory flow volume curves in neonates and infants.[1] This method was later revised and is a useful technique for investigating lung function in this age group[2 3] The technique entails compressing the chest and abdomen suddenly by using an inflatable jacket so that the compression coincides with the beginning of expiration.

The flow volume loop produced by this manoeuvre can be analysed in terms of peak flow, maximum flow at functional residual capacity (VmaxFRC), and expiratory reserve volume (Fig. 1). The peak flow is not equivalent to that obtained in older children as it is taken after a tidal breath rather than a maximal inspiration to total lung capacity

The procedure is simple and well tolerated by the infants but has limitations. Firstly, the observed functional residual capacity in the early neonatal period varies from breath to breath and is maintained above the resting volume of the respiratory system, so it will therefore be influenced by the respiratory rate and postinspiratory muscle activity.[4] There is no measurement of lung volume unless helium dilution is incorporated into the method, and thus any changes in VmaxFRC and expiratory reserve volume may be due to change in the

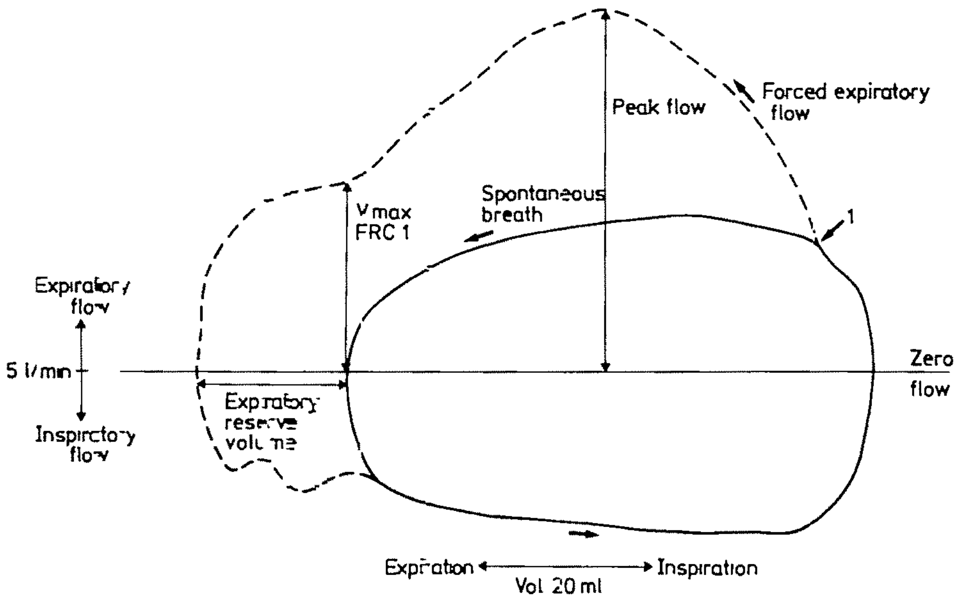

Fig. 1 *Spontaneous breath before squeeze (continuous line), start of squeeze (arrow$^1$), and forced expiratory flow volume curve (dotted line) Minimum volume of spontaneous breath defines functional residual capacity and peak flow; VmaxFRC and expiratory reserve volume are marked*

functional residual capacity from which they are calculated. Secondly, the technique assumes that the baby is relaxed during the 'squeeze ' If the baby is trying to breathe in he will be protecting his lungs against the pressure from the jacket, which may prevent the method achieving limitation flow. While using this technique we noticed that if the compression was applied late in expiration the V̇maxFRC was often higher than when the compression was applied at the beginning of expiration (Fig. 2). This should not be possible if flow is being limited. We therefore investigated babies' inspiratory efforts during the compression by using oesophageal balloons to measure intrathoracic pressure.

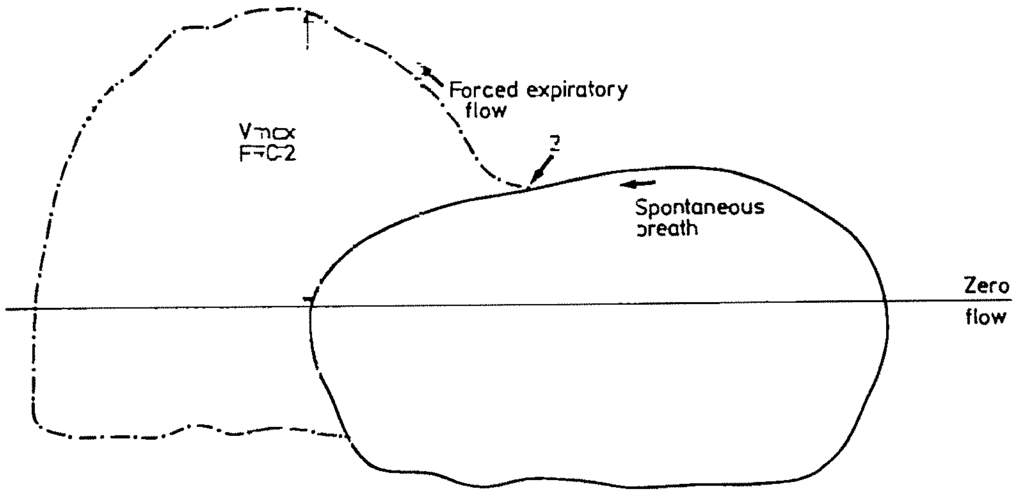

Fig. 2 *Flow volume curve from same baby as fig 1, with squeeze applied in mid-expiration (2); VmaxFRC is 30% higher than in fig 1*

## Subjects

Ten newborn babies, six boys and four girls aged 1 to 9 days (mean 3·4), were tested after oral informed consent had been obtained from the parents. Mean birth weight was 3480 g (range 2700–3800) and mean gestation 39·6 weeks (range 38–40); all the babies were clinically normal. The studies were carried out half to one hour after a feed when the babies were asleep. No sedation was given, and no attempt was made to assess the sleep state.

## Methods

Compressed air was fed into a 140 litre reservoir with a blow off valve set at 4·41 kPa (Fig. 3). This was connected by an electric solenoid switch through wide bore tubing to a Hammersmith jacket. The jacket comprised an external skin of polyvinylchloride plastic that looped round the abdomen and chest with the arms inside, and was secured with Velcro strips The anterior wall of the chest and abdomen was against the inflatable portion of the jacket, which had thick plastic on the outside and thinner plastic on the inside, resulting in the squeeze pressure being directed inwards. The pressure of the jacket was measured with a strain gauge pressure transducer (SE Laboratories 486) at the point of entry of the air into the jacket. The jacket took 110–210 ms to reach maximum pressure in vivo, and the plateau pressure was 2·74–3·63 kPa. The rise in pressure in the jacket was exponential, 63% of the maximum being reached in 10 ms.

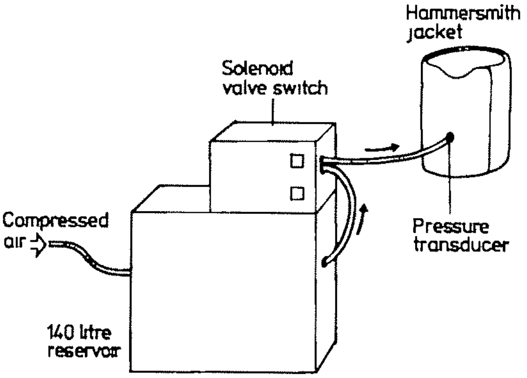

Fig 3 *Air in reservoir kept at 4·41 kPa above atmospheric pressure by a blow off valve, when valve opened, jacket inflated to about 3·43 kPa*

Flow at the mouth was measured with a Fleisch type 0 heated pneumotachograph connected to a soft rubber facemask. The pneumotachograph was linear to about 5% over the range studied (0–25 l/min).

The babies' tidal volumes were measured with a reverse plethysmograph (Fig. 4). Pressure changes in a rigid 100 litre plastic container caused by the babies' inspired and expired volumes were measured with a strain gauge pressure transducer (Pye Ether UP1).

We preferred this method of measuring volume as it was stable over each study period. Integrator drift made it difficult to identify the functional residual capacity when the integrated flow signal from the pneumotachograph was used.

The reverse plethysmograph was calibrated by injecting and withdrawing known volumes of air at

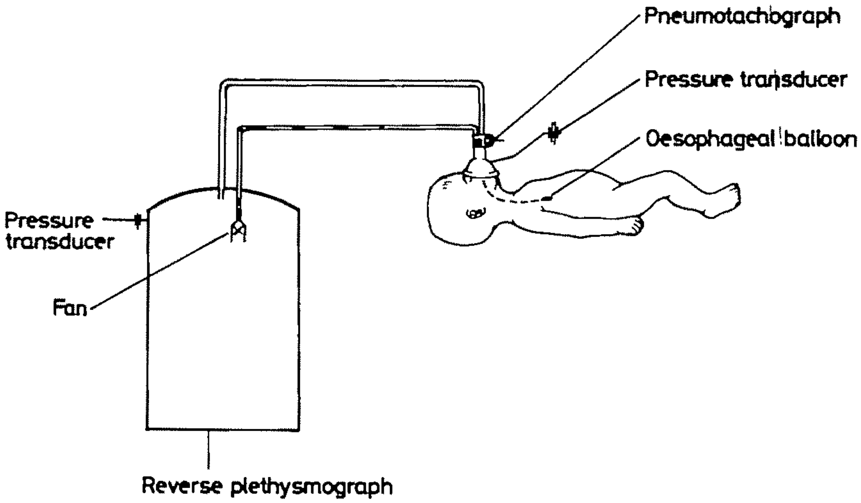

Fig 4 *Air circulated round reverse plethysmograph, pneumotachograph was mounted on face mask held to baby's face.*

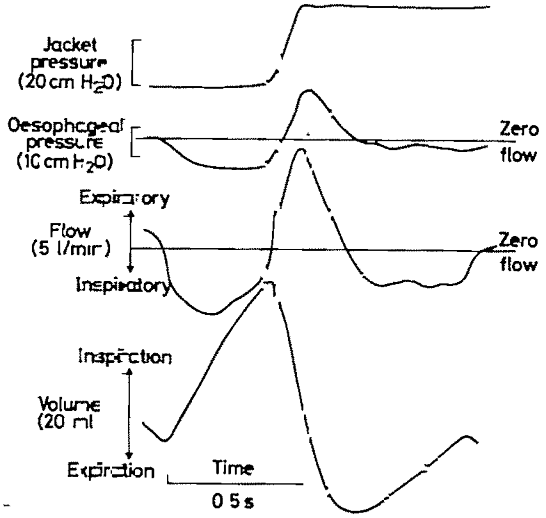

Fig. 5 *Oesophageal pressure shown in relation to jacket pressure, flow, and volume against time*

the babies' approximate respiratory rate to minimise errors due to the adiabatic effect. A fan circulated the air inside the system to reduce the dead space to 22 ml. Intrathoracic pressure was measured by an oesophageal balloon and standard techniques.[5] In the last five babies the oesophageal pressure was confirmed by occluding air flow in and out of the mask for a few seconds. In such a closed system the oesophageal pressure is the same as the mask pressure and the swings in pressure can be measured as the baby attempts to breathe.[6] The signals were amplified (SE Laboratories EMMA amplifier) and recorded on a four channel Racal tape recorder. The flow volume data were displayed on an oscilloscope to time the squeeze to the babies' breathing. At the end of the study jacket pressure, oesophageal pressure, and flow and volume signals were displayed against time by using an oscillograph (SE Laboratories 3006) and flow volume loops were drawn out on an X/Y plotter (Philips PM8041) at 25% of the original speed.

## Results

Two hundred and twenty one separate loops were obtained from 10 babies in the study, with the squeeze applied at different points in the respiratory cycle. Peak flow, expiratory reserve volume, and VmaxFRC were measured, and in 213 cases an adequate oesophageal trace was obtained. For the five babies in whom the ratio of oesophageal to mouth pressure was measured the values obtained were all within 10% of unity. Functional residual capacity was defined as the minimum lung volume from the breath before the squeeze. Table 1 shows the results for squeezes at full inspiration. These are similar to the results of other workers. In three babies the VmaxFRC was highest when the squeeze was applied in mid-expiration. By contrast, when the squeeze was applied as the babies breathed in or at functional residue capacity the flow trace was usually erratic and the peak flow much lower than expected

When the oesophageal pressure traces were examined in relation to the squeeze all traces showed an initial rise in pressure corresponding to the rise in pressure inside the jacket. In 188 cases (88%) there was a peak followed by an immediate fall in oesophageal pressure indicating inspiratory muscle activity against the squeeze (fig 5). The mean (SD) time taken to reach this peak oesophageal pressure was 155 (36) ms (range 53–302) The large variation in the peak oesophageal pressure from 0·05–2·55 kPa above atmospheric pressure meant that in many cases the inspiratory effort must have

Table 1 *Analysis of flow volume loops*

| *Case No* | *No of inflations* | *Mean (SD) peak flow (l/min)* | *Mean (SD) expiratory reserve volume (ml)* | *Mean (SD) VmaxFRC (l/min)* | *Single highest value of VmaxFRC for each baby* |
|---|---|---|---|---|---|
| 1 | 6 | 12·5 (2·2) | 12·2 (5·4) | 6·8 (2·1) | 9·9 |
| 2 | 5 | 7·4 (1·3) | 14·8 (2·6) | 5·2 (1·4) | 7·3 |
| 3 | 3 | 13·8 (1·8) | 22·2 (3·1) | 13·3 (1·8) | 15·7 |
| 4 | 10 | * | 15·4 (4·5) | 12·5 (1·3) | 14·4 |
| 5 | 2 | 13·6 (0·5) | 22·6 (1·3) | 12·2 (0·5) | 12·6 |
| 6 | 9 | 15·3 (1·9) | 16·5 (3·6) | 11·3 (1·8) | 15·5 |
| 7 | 7 | 8·2 (0·5) | 16·9 (5·0) | 7·4 (1·3) | 11·5 |
| 8 | 7 | 13·3 (2·0) | 17·2 (8·3) | 8·3 (2·1) | 11·3 |
| 9 | 4 | 12·0 (1·9) | 14·2 (2·8) | 9·4 (1·6) | 10·9 |
| 10 | 7 | 14·3 (1·6) | 19·7 (5·4) | 9·5 (3·4) | 15·6 |

*Mean not available as signal strength exceeded maximum input for several traces begun before the peak was reached. The starting point of this effort was obscured by the rise in transmitted pressure from the jacket.

On the 25 other occasions there was a plateau in the oesophageal pressure before the inspiratory effort began. The importance of these traces is that they might represent a truly passive response to the squeeze. In no case, however, was a plateau associated with a satisfactory flow volume curve. The mean (SD) time from the initial rise in the jacket pressure to the start of inspiratory effort was 291 (77) ms (range 190–536). Eighteen of these 25 responses were from two babies. The presence of a plateau was not related to the timing of the squeeze in the respiratory cycle. In the two babies with the repeated plateau traces we looked at the percentage of the squeeze pressure transmitted to the oesophageal balloon. With the exception of one value from each baby the results were reproducible. When those two low results were excluded the mean percentage transmission of pressure across the chest wall was 57·9 and 67 (cases 2 and 5, respectively, in Table 1). The results from case 5 were all associated with zero flow, which implies glottic closure, and this was a common response to inflation of the jacket in this baby (12 out of 22 squeezes). In case 2 all the flow traces showed erratic expiratory flow when an oesophageal plateau was present, implying downstream narrowing (presumably partial glottic closure) During the remaining seven squeezes in three infants one achieved 78% transmission of jacket pressure, which was associated with air flow obstruction, but in the six others the percentage ranged from 9 to 54, indicating some degree of inspiratory effort against the squeeze in most if not all of these plateaus.

To assess whether the timing of inflation pressure in the respiratory cycle influenced the speed and magnitude of the response the mean of the two previous tidal breaths was used to calculate the length of the respiratory cycle. If these two breaths varied by more than 0·3 s the result was discarded, 0·3 seconds represents 20% of the respiratory cycle in a baby breathing at 40 breaths a minute and was enough to exclude squeezes for which the baby's respiratory pattern was changing appreciably from breath to breath. The time from full inspiration to the start of the jacket squeeze was then expressed as a percentage of a full respiratory cycle, 0% and 100% representing full inspiration. Table 2 shows the results for inflations around full inspiration (80–100% and 0–20%) against inflations around full expiration (30–70%). The time taken for the jacket pressure to rise was similar in the two groups ($t$ = 0·98, $p > 0·2$, paired $t$ test). At lower lung volumes the peak oesophageal pressure was significantly earlier and significantly smaller.

## Discussion

The object of the forced partial expiratory flow volume technique is to give a transthoracic pressure that is high enough to limit flow. Once this critical pressure is exceeded the flow depends only on the conformation of the airways and the degree of inflation of the lungs. The variation in this flow limitation is then used to indicate abnormalities of the lungs[3 7] We have shown a reflex inspiratory response to external compression of the chest that may interfere with these measurements. This would explain the anomalous finding of supramaximal flow when the squeeze is applied during expiration and would mean that values of VmaxFRC are underestimated and depend partly on the strength of the reflex. The reflex is more obvious at low lung volumes, although accurate timing of onset is not possible when an oesophageal balloon is used as it reflects intrathoracic pressures rather than muscular effort. Diaphragmatic electromyographic recordings are needed to pinpoint the start of the reflex but have the disadvantage of not being quantitative.

This response to chest compression has been observed during the resuscitation of the newborn, when it is a powerful stimulus for a deep inspiratory effort in asphyxiated babies.[8] Pulmonary rapidly adapting receptors (irritant receptors) stimulate

Table 2 *Relation of onset of inspiratory effort and peak oesophageal pressure to time of inflation (values are means (SE))*

| | *Top of tidal breath* | *Bottom of tidal breath* | *t test* |
|---|---|---|---|
| Time to observable inspiratory effort (ms) | 176 (5) (n = 128) | 139 (5) (n = 46) | p = <0·001 (95% confidence interval for magnitude of difference = 23 to 51 ms) |
| Peak oesophageal pressure (kPa) | 1·69 (0·06) (n = 116) | 0·94 (0·08) (n = 42) | p = <0·001 (95% confidence interval for magnitude of difference = 0·58 to 0·91 kPa) |

phrenic activity in response to lung deflation in rabbits,[9] and this reflex presumably plays a part in the gasping inspirations of newborn babies.[10] The same mechanism is probably responsible for our results. Babies always make some response to try to limit the effect of the squeeze, using either the diaphragm and chest wall or the glottis, and we conclude that further elucidation is needed before partial forced expiratory flow volume loops can be interpreted easily

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# Morbidity after percutaneous liver biopsy

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SUMMARY The safety of percutaneous liver biopsy with a 1·2 mm Menghini needle in infants aged one year or less was investigated. One hundred and eighty four procedures performed from 1975 to 1985 were reviewed. There were no deaths or major complications within 48 hours associated with the procedure. In five instances specific complications occurred: a drop in haemoglobin concentration (three), transient hypotension (one), and haematoma at the biopsy site (one). The result of liver biopsy was diagnostic in 83% of cases, compatible with unspecified metabolic disease in 8%, and normal or not diagnostic in 9%. This study suggests that percutaneous liver biopsy can be performed with relative safety in small infants if coagulation is normal and there are no major contraindications, and the results yield important diagnostic information which cannot be obtained using less invasive procedures.

Percutaneous needle biopsy of the liver is an important procedure in diagnosing liver disease in infants as it often provides diagnostic information not obtainable by other methods.[1 2] The technique has been widely used in adults for over 30 years. Recent reports have confirmed the low incidence of complications of liver biopsy as long as results of coagulation tests are normal.[3–5] Percutaneous liver biopsy was first reported in children in the late 1950s[6–9] and is regarded as safe in this age group.[10] The safety of this procedure in infants, however, is sometimes questioned. No recent series to our knowledge specifically examines the mortality and morbidity in children less than 1 year old.

We studied the safety of percutaneous liver biopsy in infants and report the morbidity in children aged 1 year or less at this hospital from 1975 to 1985.

## Methods

The hospital records of all children aged 1 year or less who underwent a percutaneous liver biopsy from 1975 to 1985 were reviewed. Data collected before biopsy included age and weight of the patient, haemoglobin concentration, platelet count, prothrombin time, partial thromboplastin time, and presence of ascites. The Menghini technique with minor modifications was used for all biopsies.[11–12] The liver biopsy needle was 1·2 mm in diameter. The number of attempts at biopsy required to obtain an acceptable specimen was recorded when reported. The histological diagnosis was noted

Morbidity within 48 hours of biopsy was assessed by examining the hospital chart for the following information: haemoglobin concentration before and after biopsy; need for transfusion after the biopsy; acute change in clinical state, excessive irritability, abdominal distension, or fussiness; difficulty in breathing or pneumothorax; gradual deterioration of clinical state including worsening of liver function test results; fever, infection, or peritonitis; and abnormal vital signs.

## Results

One hundred and eighty four consecutive needle biopsy procedures in 174 children were reviewed. Table 1 summarises ages and weights of the patients reviewed. The median age was 3 months. Twenty

Table 1 *Summary of age and body weight of 184 patients undergoing liver biopsy*

| *Age group (months)* | *No of biopsies* | *Mean weight (kg)* | *Weight range (kg)* | *% Of total No of cases* |
|---|---|---|---|---|
| < 1 | 16 | 3·36 | 2·7 – 4·3 | 8·7 |
| 1 – < 2 | 36 | 3·32 | 1·2 – 5·7 | 19·6 |
| 2 – < 3 | 35 | 4·12 | 2·6 – 5·3 | 19·0 |
| 3 – ≤ 6 | 61 | 5·11 | 2·1 – 10·2 | 33·2 |
| Total ≤ 6 | 148 | | | 80·4 |
| Total group | 184 | 4·81 | 1·2 – 14·1 | 100·0 |

seven infants weighed ≤ 3 kg and three of these were < 2 kg.

Liver biopsy was tolerated well by the children, and no deaths occurred In addition, no child developed haemoperitoneum, haemothorax, bile peritonitis, pneumothorax, or sepsis.

In five children specific complications occurred (Table 2). Three had a drop in haemoglobin concentration, for which two were given transfusions Only one of these was symptomatic A further patient with haemoglobin concentration before the procedure of 8·7 g/dl had an episode of hypotension after the biopsy; no treatment was required, and we did not know whether this reflected bleeding or sensitivity to the sedation. One child developed a small subcutaneous haematoma at the biopsy site, it resolved without treatment.

Patients with a potentially higher than average risk of morbidity after liver biopsy include very small infants, those with anaemia, and, as shown in previous studies in adults, those with thombocytopenia, abnormal coagulation test results, or severe ascites. Twenty six of the 27 children weighing ≤ 3 kg had no complications; one infant, who weighed 2·7 kg, had a drop in haemoglobin concentration. In the entire series there were 21 patients with haemoglobin concentrations < 9·5 g/dl; none experienced any difficulties except the child with transient hypotension. No complications occurred in seven patients with platelet counts ranging from 60 to 90 × $10^9$/l or in one patient with a platelet count of 48 × $10^9$/l. Three children had abnormal results of coagulation tests (prothrombin time > 14 seconds; partial thromboplastin time > 47 seconds). Two were given vitamin K or fresh frozen plasma before the biopsy and one received no supplementation: none had a complication Three children had obvious

Table 1 *Histological diagnoses in 174 patients*

| *Diagnosis* | *No of cases* |
|---|---|
| Idiopathic neonatal hepatitis | 45 |
| Extrahepatic biliary atresia | 41 |
| α-1-Antitrypsin deficiency | 9 |
| Cholestasis associated with total parenteral nutrition | 13 |
| Alagille's syndrome | 4 |
| Cytomegalovirus infection | 5 |
| Galactosaemia | 3 |
| Cystic fibrosis | 1 |
| Glycogen storage disease | 6 |
| Zellweger's disease | 3 |
| Hereditary fructose intolerance | 2 |
| Metabolic disease, no specific diagnosis | 14 |
| Reye's-like syndrome | 2 |
| Miscellaneous | 20 |
| Normal, no pathological diagnosis | 7 |

One infant underwent biopsy twice neonatal hepatitis diagnosed on first, and extrahepatic biliary atresia on second, biopsy

Table 2 *Details of patients with complications after liver biopsy*

| *Case No* | *Age (months)* | *Weight (kg)* | *Underlying diseases* | *Prothrombin time, partial thromboplastin time, platelet count ($10^9$/l)* | *Ascites present* | *General anaesthetic* | *Clinical course* |
|---|---|---|---|---|---|---|---|
| 1 | 2·5 | 3 6 | Transposition of great vessels, mitral atresia, pulmonary stenosis, Blalock-Taussig shunt, intravenous nutrition | 13·7, 35 9, 158 | Yes | No | Patient moved during biopsy, hypotension, tachycardia, drop in haemoglobulin concentration necessitating blood transfusion |
| 2 | 1 | 2 7 | Neonatal hepatitis | 9 6, 35 1, 323 | No | No | Routine procedure, no distress after biopsy, drop in haemoglobulin concentration necessitating blood transfusion |
| 3 | 5 | 4 1 | Hepatomegaly, malabsorption | 10 5, 26·7, 397 | No | Yes | Routine procedure, no distress after biopsy |
| 4 | 3 | 4 4 | Neonatal hepatitis | 10·5, 38·4, 192 | No | No | Routine procedure; hypotension two hours after biopsy, increased intravenous fluid replacement, recovery |
| 5 | 7 | 4 8 | Neonatal hepatitis | 10 2; 39 3, 412 | No | No | Routine procedure, haematoma at site of biopsy five to six hours later, no distress |

ascites at the time of biopsy One had a fall in his haemoglobin concentration after biopsy, which required a blood transfusion. Two had no complications. Thus even those infants at increased risk tolerated the procedure well.

The number of attempts was noted in only 73 instances. One attempt was made in 43, two in 27, and three in three. There was no increase in complications associated with multiple attempts.

The liver biopsy specimen was diagnostic in 146 (83%) cases, and the histological diagnoses are summarised in Table 3. Apart from idiopathic neonatal hepatitis and changes consistent with extrahepatic biliary tract obstruction (most probably extrahepatic biliary atresia), metabolic disease predominated. Miscellaneous diagnoses included fibrosis or cirrhosis of uncertain aetiology and myeloproliferative or neoplastic disease. Two patients showed progression from neonatal hepatitis to fibrosis or cirrhosis in serial biopsy specimens.

## Discussion

These data show that percutaneous liver biopsy is safe in infants. Nearly all babies were active and eating within one to two hours after the procedure.

The safety of percutaneous liver biopsy in adults has been discussed on many occasions[13-15], the most recent large study reported a mortality of 0·005% with the Menghini technique [5] Serious complications included bleeding from the liver (causing haemoperitoneum or haemothorax), pneumothorax, bile peritonitis, and sepsis. Liver biopsy can also cause traumatic haemobilia.[16] Complications occur most commonly within the first 10 hours after biopsy; in a large study in adults only 4% of complications occurred later (one to six days after the procedure) [5] Intrahepatic haematoma may be asymptomatic [17-18] Percutaneous liver biopsy can be performed in adults with extrahepatic biliary obstruction with a low incidence of complications.[19] The possible presence of a tumour or congestion is not necessarily a contraindication.[20]

Liver biopsy has been adopted as a procedure in children without the same extensive examination of its safety as in adults. Reports from the late 1940s of large numbers of children being investigated for malnutrition suggested that percutaneous liver biopsy by a subcostal approach was safe.[21] Early reports of small series in children using either the Vim Silverman or the Menghini technique showed no major complications [6-9] Walker *et al* reported no life threatening complications in a series of 210 biopsies performed in 166 patients, of whom 67 were aged 1 year or less and 24 were aged 1 week to 2 months.[10] Three minor complications were reported in the entire series, but the ages of the patients were not stated In a prospective study of the risks of certain procedures in children Ament found a rate of complications of 4% in 584 liver biopsies performed at 25 centres in 1978 [22] These complications included bleeding, pneumothorax, and pain; clinical details including ages of the patients, number of infants with and without complications, condition of patients, and biopsy technique were not given.[22]

In infants the indications for liver biopsy are similar to those in adults. Severe cholestasis is not a contraindication to liver biopsy in this age group, although in most cases ultrasound examination of the liver will have been performed before biopsy to exclude the presence of cysts or large bile lakes likely to be punctured by the biopsy needle. Likewise liver congestion per se is not a contraindication. Any highly vascular mass such as a haemangioma, arteriovenous malformation, or vascular liver tumour, however, is not suitable for percutaneous liver biopsy, neither should biopsy be done if there is infection of the adjacent lung, pleura, or skin, or peritonitis

Both in infants and adults some complications of liver biopsy can be avoided if patients at high risk of bleeding are excluded. Despite claims that hepatic bleeding after biopsy is a random event[23] patients with abnormal results of clotting studies seem to be at risk. Although no patients in our series underwent biopsy if the prothrombin time was > 15 seconds or the partial thromboplastin time was > 49 seconds, 15 infants with slightly abnormal coagulation profiles did so. Some patients received fresh frozen plasma at the time of the liver biopsy.[24] The platelet count was $> 60 \times 10^9/l$ in all but one In individual patients it may be necessary to estimate bleeding time before biopsy to be certain of adequate platelet function when there is reason to suspect thrombasthenia despite a normal platelet count. Severe ascites makes the liver difficult to biopsy and may interfere with haemostasis. In our series only three patients with obvious ascites underwent biopsy.

In adults the theoretical risk of this procedure has been determined by pooling individual series of liver biopsies. Data on infants from other studies in which the Menghini method was used are difficult to interpret because of insufficient information, and if these are added to our series they raise the total number of infants to about 250, which is still too small to eliminate the β error entirely.[9-10] Our data from one centre with only one biopsy technique suggest that percutaneous liver biopsy is safe in infants. The rate of minor complications was 2·7%. Recently there has been some enthusiasm for performing liver biopsies in adults as an outpatient procedure.[4 25] We do not think that our data can be extended to support a policy of routine outpatient liver biopsy for infants.

The decision about whether to perform a liver biopsy in an infant should be based on the usefulness of the histological information to be gained as well as on technical considerations. Delay in diagnosis of liver disease in infants can have serious consequences. Liver biopsy specimens are prepared at this hospital for histochemical studies and light and electron microscopic examination. We obtained diagnostically important information in 83% of cases.

We conclude that a percutaneous liver biopsy performed by the Menghini technique is safe even in small infants. The patient should have normal coagulation and there should be no other major contraindications to the procedure. Ultrasound examination of the liver should be performed before liver biopsy. Potentially vascular lesions should not be biopsied percutaneously. The relative risks and benefits of percutaneous liver biopsy in infants weighing <2 kg should be carefully considered. Young age or small body size, however, are not in themselves high risk exclusion criteria for this procedure.

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# Prospective study of serum staphylococcal antibodies in cystic fibrosis

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SUMMARY Serum IgG antibodies to teichoic acid and alpha toxin from *Staphylococcus aureus* were measured in 62 patients with cystic fibrosis by enzyme linked immunosorbent assays. The patients were followed up for 12–24 months in a prospective study. Raised titres were found exclusively in patients chronically colonised with *S aureus*. Patients colonised with both *S aureus* and *Pseudomonas aeruginosa* had significantly higher titres against teichoic acid than those carrying *S aureus* alone. Titres were significantly higher when there were clinical signs of low grade infection in the patients chronically colonised with *S aureus* alone, and in those with both *S aureus* and *P aeruginosa*. Significant reduction in titres occurred after antimicrobial treatment given either orally or intravenously in patients with normal erythrocyte sedimentation rates and white cell counts. Measurement of staphylococcal antibody titres may be valuable in monitoring pulmonary infection and antimicrobial treatment in patients with cystic fibrosis.

The major factor in determining the severity of illness and mortality in patients with cystic fibrosis is still chronic respiratory tract infection.[1] The predominant organisms isolated from sputum in these patients are *Staphylococcus aureus* and *Pseudomonas aeruginosa*.[2] The prognosis after colonisation with *P aeruginosa* is poor.[3] Colonisation by *P aeruginosa* is usually preceded by colonisation by *S aureus* for varying lengths of time.[1] The extent of lung damage caused by *S aureus* and its role in the progression of the disease is still not clear.[4] Different views are reflected in the treatment regimens given which range from no treatment (to protect from an overgrowth of *P aeruginosa*),[5] long term prophylaxis,[4 6] or intensive treatment to eradicate the staphylococci.[7] Eradication of the colonising organism, however, be it *S aureus* or *P aeruginosa*, is seldom more than temporary. Meanwhile the use of antibiotics controls episodes of overt infection.[8–10]

There is no consensus about when to prescribe antibiotics [4 10] Our policy, which is to begin treatment in the initial stage of infection, is difficult in cases when the erythrocyte sedimentation rate and white cell count are normal.

New serological tests have recently shown a rapid antibody response to staphylococcal antigens, which raises the possibility of identifying patients in need of treatment.[11] Enzyme linked immunosorbent assays (ELISAs), using purified staphylococcal teichoic acid and alpha toxin as antigens, have improved the sensitivity of serology in the diagnosis of septicaemia and deep staphylococcal infections.[12] We have previously used these assays in patients with cystic fibrosis and found increased titres to both antigens only in patients colonised with *S aureus*, and particularly those receiving inadequate doses of antibiotics.[13] These observations initiated a long term prospective investigation of the changes in antibody titres associated with colonisation, early signs of active infection, and the effect of treatment with antibiotics in patients with cystic fibrosis.

## Patients and methods

### PATIENTS

Sixty two patients with cystic fibrosis, aged from 4 months to 32 years (mean and median 12·5 years), were studied. The diagnosis was made by the sweat test (chloride > 80 mmol/l) and typical pulmonary symptoms. All patients but one had pancreatic insufficiency. All patients were followed up monthly. The patients were classified into four groups according to the results of sputum cultures.

*Group A* comprised 18 patients, aged 6 to 27 years (mean 14 years) who were chronically colonised with *S aureus*—that is, *S aureus* was repeatedly present in the sputum during the six months preceding the study. In 10 patients *Escherichia coli*, *Klebsiella* species, *Haemophilus influenzae* and *Pseudomonas maltophilia* were also occasionally found. A total of 133 samples were analysed from this group.

*Group B* comprised 16 patients, aged 2 to 26 years (mean 15 years) who were chronically colonised with *S aureus* but who were also either chronically colonised (13 patients) or occasionally colonised with *P aeruginosa* (three patients). One hundred and sixty two samples were analysed from these patients

*Group C* comprised 14 patients, aged 6 to 32 years (mean 17 years) who were chronically colonised with *P aeruginosa*. Cultures from five patients had also grown *S aureus* occasionally, and those from one patient grew *E coli* intermittently during the study period One patient was chronically colonised with *E coli*. A total of 155 samples were analysed

*Group D* comprised 14 patients aged 4 months to 5 years (mean 2·2 years) who were too young to collect sputum. Nasopharyngeal cultures occasionally grew *H influenzae*, *S aureus* (10 patients), and *Haemophilus parainfluenzae* but never *P aeruginosa*. Thirty three samples were analysed.

The study was originally designed to last a year but for most of the patients (44 of 62 or 71%) the study was continued for another year Earlier samples were also available from 25 patients (40%), resulting in a follow up of 24 to 94 months.

The clinical score was recorded according to Shwachman excluding the *x*-ray score; thus a maximum of 75 indicated an excellent clinical condition.[14] The clinical scores ranged from 30 to 75 (mean 61, median 63) at the beginning of the study The pulmonary *x*-ray pictures were evaluated by a modified Norman-Chrispin score.[15] The mean *x*-ray score was 3 (median 3, range 0–12); a value of 0 indicated a normal picture and a maximum of 16 severe disease. Forced expiratory volume in one second was measured at least once a year in patients older than 5 years and expressed as the percentage of predicted values for age.[16] This averaged 67% (median 65, n = 39, range 20–111) at the first investigation of the patients during the study period.

Clinical signs and symptoms of infection such as change in the volume and appearance of the sputum, increased respiratory rate, dyspnoea, increasing abnormalities on chest auscultation, increasing cough, decreased appetite, weight loss, and deterioration in the results of standard biochemical tests were used to indicate the necessity for antimicrobial treatment. The classification of the patients as 'infected' or 'non-infected' was based on the presence of two or more of these criteria. In most cases the clinical signs of infection were discreet and not parallelled by raised erythrocyte sedimentation rate or white cell count. Fever was seldom present.

During the two year study, 81 courses of intravenous antibiotics were given to patients in groups A–C The effects of treatment on antibody titres were determined in blood samples taken at the start and the end of the courses, the average interval being 13 (range 9–29) days. Sixteen courses of treatment were given to six patients harbouring only *P aeruginosa*, while the remaining courses (n = 65) were given to patients chronically or occasionally colonised with *S aureus*. Chemotherapy was based on the resistance pattern of the bacteria.[17,18] Cephalosporins either alone or in combination with an aminoglycoside accounted for 63% of the total intravenous courses and 55% of the intravenous courses given to the patients harbouring *S aureus*. The remaining intravenous courses comprised ampicillin, cloxacillin, imipenem, or a ureidopenicillin. Furthermore, some patients were frequently treated orally with flucloxacillin alone or with pivampicillin or trimethoprim and sulphamethoxazole.

Capillary or venous blood samples were taken from all patients at least once a year, giving a total of 484 samples during the study. In most cases samples were obtained before and after a period of antibiotic treatment (n = 222). Sera were frozen at − 20°C until analysed. All sera from each patient were analysed at the same time

ELISA for IgG antibody determinations to teichoic acid[13,19] and to alpha toxin[13,20] have been described in detail before. Briefly, cobalt irradiated polystyrene microplates (Dynatech M 129B, Plochingen, West Germany) were coated overnight with teichoic acid (2 μg/ml) or alpha toxin (5 μg/ml). Patients sera were tested in duplicate in dilutions of 1/1000 or 1/10000, incubated for one hour, and then overnight with alkaline phosphatase conjugated swine antiserum to human IgG antibodies (Orion Diagnostica, Finland). All incubation was done at room temperature (22°C). 100 μl volumes were used throughout and all washings were done three times.

The titre measured by the ELISA was defined as the absorbance value at A405 nm multiplied by the serum dilution factor—that is, $10^3$ or $10^4$. Known positive and negative controls (three patients and three healthy controls) were included in each test series and the results were corrected against these controls to minimise day to day variation. The coefficients of variation were 5–10% (intra-assay) and 10–15% (interassays).

The upper limit of normal values had previously been established in a healthy population of different ages[19,20] As the titres showed definite variations with age the upper cut off point was set at the mean (2 SD) for different age groups, corresponding to about the 95th percentile of the normal population Consequently, a diagnostic titre in one age group could represent a normal value in another age group. Due to the long observation period in some children, different cut off points had to be applied for samples at different times in the same patient. The ELISA titres are therefore presented as multiples of the upper limit of normal values for the relevant age group, which was set at 1. As the upper limit of normal was set at mean (2 SD) the mean titres in the healthy population ranged from 0·35 to 0·5 in the different age groups. Multiples of more than 1 were considered to be diagnostic

The $\chi^2$ test with Yates's correction, the Mann-Whitney U test and the Wilcoxon matched pairs signed ranks test were used to assess differences in proportions.

## Results

### CLINICAL MEASUREMENTS

Over the study period there was no change in the average values of clinical score, *x* ray score or readings of forced expiratory volume in one second, in the whole group of patients, indicating stable disease. The patients classified as 'non-infected' had a normal mean white cell count of 6·8 × $10^9$/l (n = 156, range 2·1–13·6) and normal erythrocyte sedimentation rate of 13 mm in the first hour (n = 143, range 1–37) Most patients showed only slight symptoms of infection when classified as 'infected'—for example, loss of appetite, increased coughing—with only a slight increase in white cell count (mean 9·7 × $10^9$/l, n = 126, range 2·4–20·5), and erythrocyte sedimentation rate of 20 mm in the first hour (n = 117, range 2–112).

The 81 intravenous courses of antibiotics, mostly prescribed for low grade infection, resulted in clinical improvement with reduced sputum and increased body weight. A decrease in white cell count from 9·8 × $10^9$/l (n = 59, range 2·4–19·1) before treatment to 7·1 × $10^9$/l (range 2·1–14·1) after treatment was noted (p < 0·001) There was no corresponding fall in erythrocyte sedimentation rate (the mean value being 17 mm in the first hour before and 16 mm after treatment) Values for forced expiratory volume in one second showed significant improvement after antimicrobial treatment, increasing from 57% (n = 32, range 18–99) to 68% (range 19–110) p < 0·001.

### ANTIBODIES TO TEICHOIC ACID

IgG antibody titres to teichoic acid were determined in 484 serum samples from the 62 patients (1–30 samples for each patient). Fig. 1 shows the distribution of titres in each group in relation to clinical signs of infection Most patients are represented once as 'infected' and once as 'non-infected'. Diagnostic titres (above 1) were found exclusively in patients chronically colonised with *S aureus* alone or in combination with *P aeruginosa* (groups A and B compared with groups C and D, p < 0·01). The titres were significantly higher in the 'infected' patients compared with those in the 'non-infected' group (p < 0·02). One patient in group D, whose nasopharyngeal culture repeatedly yielded *S aureus*, had a slight increase in antibody titre. Three patients with dual colonisation (group B) were the only 'non-infected' patients with diagnostic titres (Fig. 1)

When analysing the results of all 484 samples, titres above the normal ranges for age were found in 29% of the sera from patients chronically colonised with *S aureus*, 17% in group A and 36% in group B (Fig. 2a). The mean titres were significantly higher in patients chronically colonised with *S aureus* (groups A and B, 0·6 and 1·5, respectively), compared with those who were not (groups C and

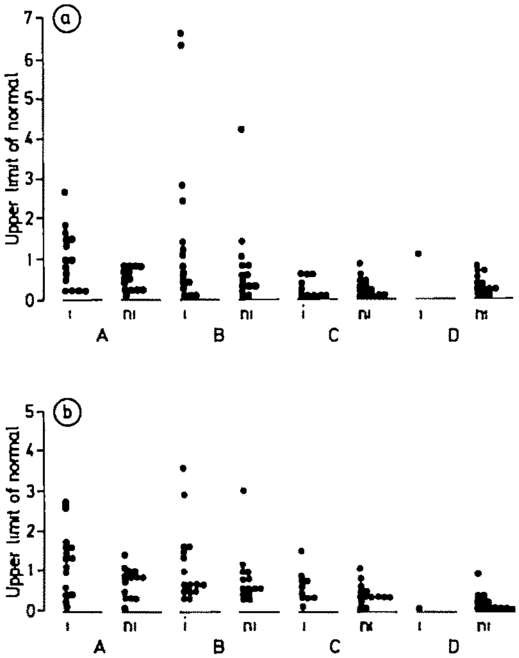

Fig 1a and b *Serum titres of IgG antibodies to staphylococcal teichoic acid (1a) and α toxin (1b) in groups A, B, C, D, i = infected· ni = not infected*

D, 0·3 and 0·4, respectively, $p < 0\cdot001$). The difference in mean titres between groups A and B was also significant ($p < 0\cdot001$)

The frequency with which diagnostic titres were found varied with clinical signs of infection, 7% in group A and 29% in group B when the patients were 'non-infected'—and rising at the time of symptomatic infection to 38% ($p < 0\cdot001$) and 47% ($p < 0\cdot02$), respectively. The titres were also significantly higher in 'infected' patients in group A and B, 1·0 and 2·1, compared with those who were 'non-infected', 0·5 and 1·2 ($p < 0\cdot001$ and $p < 0\cdot01$, respectively).

### ANTIBODIES TO ALPHA TOXIN

The serum samples were also analysed by ELISA for IgG antibodies to alpha toxin. Fig 1b shows the distribution of titres in the different patient groups. Again, pathological titres were almost exclusively found in patients chronically colonised with *S aureus* with or without *P aeruginosa* ($p < 0\cdot001$ when groups A and B were compared with groups C and D) 'Infected' patients had a significantly larger number of diagnostic titres than those not clinically infected (48% *v* 14%, $p < 0\cdot02$).

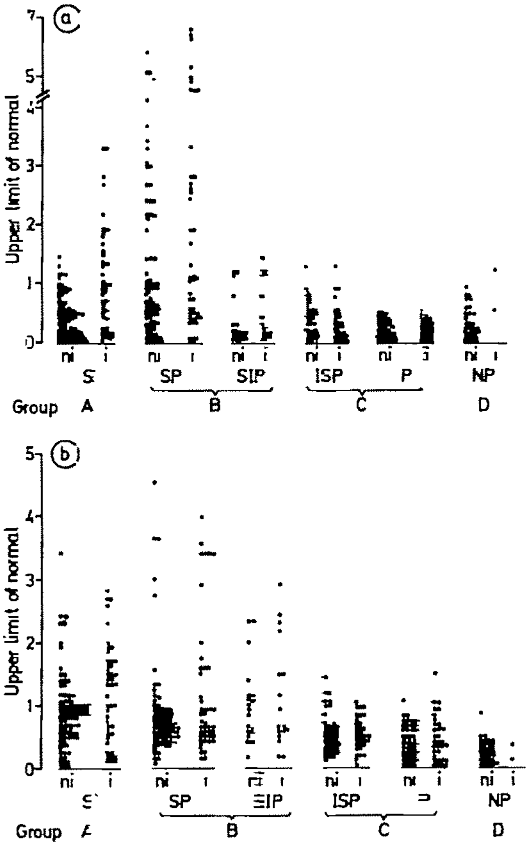

Fig. 2a and b *Serum titres of IgG antibodies to staphylococcal teichoic acid (2a) and α-toxin (2b) S = chronic S aureus; SP = chronic S aureus and P aeruginosa; SIP = chronic S aureus and occasional P aeruginosa, ISP = occasional S aureus and chronic P aeruginosa, P = chronic P aeruginosa, NP = nasopharyngeal culture.*

Raised antibody titres were found in 29% of all the samples of patients chronically harbouring *S aureus*, 35% of samples in group A and 27% in group B (Fig 2b). Significantly higher mean titres were found in patients chronically colonised with *S aureus*, groups A and B (1·0 and 1·0, respectively) compared with groups C and D (0·5 and 0·2, $p < 0\cdot001$, respectively). 'Infected' patients in groups A and B showed higher mean titres, 1·2 and 1·2, then those clinically 'non-infected' (0·9 and 0·9, $p < 0\cdot02$, respectively)

Diagnostic titres (> 1) were found in 26% of samples from 'non-infected' patients in group A, the number rising to 53% when 'infected' ($p < 0\cdot01$) The corresponding figures for group B were 21% and 35%, respectively ($p < 0\cdot05$) One patient (two samples) had slightly increased serum titres to alpha toxin despite the absence of *S aureus* from his sputum (group C). This patient had been chronically colonised with *S aureus* for many years before sampling, the last positive sputum culture being one year before the study.

Diagnostic titres (> 1) to both teichoic acid and alpha toxin were found in 11 patients (32%), a total of 9% of the samples. Three patients had diagnostic titres only to teichoic acid, and another eight patients exclusively to alpha toxin. Twelve (35%) of the 34 patients who were chronically colonised with *S aureus* never showed diagnostic titres to either teichoic acid or alpha toxin, some not even during a seven year observation period.

### ASSOCIATION BETWEEN ANTIBODY TITRES AND ANTIMICROBIAL TREATMENT

Increases in antibody titres usually related to clinical infection while decreases occurred after antimicrobial treatment. Figs. 3 and 4 show two examples of typical patterns of antibody responses to both teichoic acid and alpha toxin in association with both oral and intravenous antibiotic treatment

In the six patients harbouring only *P aeruginosa* the serum titres against staphylococcal antigens were within normal ranges and were not significantly influenced by the 16 courses of antibiotics. The remaining 65 courses given to patients colonised with *S aureus* resulted in significant decreases in titres to both teichoic acid ($p < 0\cdot01$) and alpha

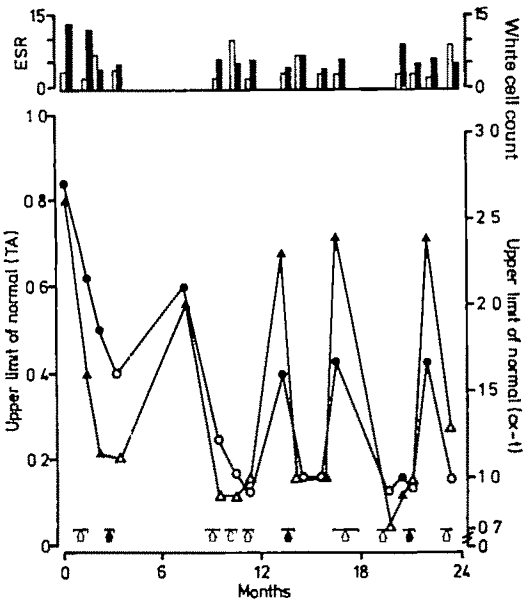

Fig. 3 *Serum antibody titres to teichoic acid, TA (O) and α toxin, α t (Δ) and antibiotic treatment in boy aged 12 with S aureus and P maltophilia Open arrows—oral treatment; closed arrows—intravenous treatment, solid bars—white cell count; open bars—ESR*

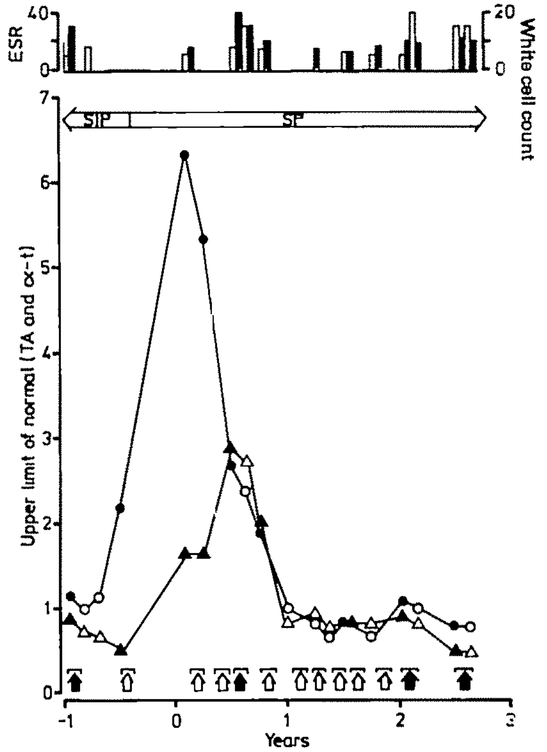

Fig 4 *Serum antibody titres to teichoic acid (O) and α toxin (Δ) in relation to change in colonisation, infection and antibiotic treatment in a boy of 3 Open arrows—oral treatment; closed arrows—intravenous treatment, solid bars—white cell count; open bars—ESR.*

toxin ($p < 0{\cdot}001$). This was true for the 36 of 65 (55%) treatments with cephalosporins alone or in combination with aminoglycosides ($p < 0{\cdot}01$ and $p < 0{\cdot}001$, respectively) The remaining 29 courses of cloxacillin (eight of 29), piperacillin (six of 29), ureidopenicillin (eight of 29), and other agents (seven of 29) also resulted in decreased titres ($p < 0{\cdot}05$ for both antigens, $n = 29$). Twelve of the 22 patients with increased serum titres in groups A and B showed a return to normal titres after antimicrobial treatment. In another nine patients the titres decreased—seven to just above normal. The effect of oral antibiotic treatment on titres could only be evaluated in 28 instances. Significant decreases of titres to both teichoic acid and alpha toxin were also seen on this regimen ($p < 0.05$).

During the entire study period only one patient's serum titres did not decrease towards normal after antibiotic treatment The antiteichoic acid titres fluctuated between 4 and 7 and anti alpha toxin titres between 3 and 5, despite frequent oral and intravenous courses of antibiotics. He was one of our most seriously ill patients, although his clinical score during the study period was 48–35–50, his forced expiratory volume in one second 42–43%, and his body weight − 1·5 SD. At the age of 11 he was colonised with both *S aureus* (phage type 94/96) and *P aeruginosa*. This consistently increased antibody pattern was not seen in other patients with dual colonisation or in patients with the same phage type of staphylococci.

## Discussion

The upper limit of normal values established in the healthy population[19 20] probably reflects antibody responses on repeated contact with, or transient colonisation of, *S aureus* in the general population. This is shown by the 20-fold increase in mean titres to teichoic acid between the age of 6 months and young adulthood, necessitating the use of age correlated normal values. The additional colonisation of *S aureus* in the lungs of patients with cystic fibrosis does not seem to result in higher basic values. Diagnostic titres of serum antibodies to teichoic acid or alpha toxin, or both, were found only in patients who were chronically colonised with *S aureus*. Of these patients, 65% showed occasional diagnostic serum titres during the two years. The incidence of increased titres was significantly higher in 'infected' patients, 44% *v* 17% in 'non-infected' (p < 0·01). Interestingly, 86% of the patients with increased titres (> 1), showed a decrease compared with those found in healthy controls of the same age groups after antimicrobial treatment.

Diagnostic titres were seen almost exclusively during periods of infection. In patients with endocarditis and septicaemia due to staphylococcal infection the sensitivity of the ELISA assays was 80–90% The corresponding value was not established for other serious infections (such as pneumonia) but we would expect them to give rise to a similar antibody response. The very high titres seen in some of our 'infected' patients, similar to those seen in staphylococcal endocarditis,[19–21] support this hypothesis. The observation that only 65% of our patients with chronic *S aureus* colonisation had diagnostic titres could reflect differences in the aggressiveness of the infections. Our patients were often treated as soon as signs of infection developed, and this could have hindered the antibody response. For this reason our results might not be applicable to other centres with different policies of treatment. Furthermore, the reference methods used to evaluate the sensitivity of the ELISA are different for different infections In patients who did not have cystic fibrosis the diagnosis was verified by blood cultures, whereas in patients with cystic fibrosis the diagnosis of 'infection' was based on clinical changes which might not be due to exacerbations of the *S aureus* infection.[13–22] Of the 12 patients who were chronically colonised with *S aureus* and who had normal titres, only three were chronically colonised with *S aureus* alone.

The incidence of raised serum titres in our patients harbouring *S aureus* was similar to that in earlier studies using precipitating antibodies.[7] Precipitating antibodies were, however, not affected by treatment. The ELISA showed higher specificity, as precipitating antibodies were also reported in patients without *S aureus* in sputum cultures.

An unexpected finding was the significantly higher antibody titres to teichoic acid in patients with dual colonisation of *S aureus* and *P aeruginosa* compared with those harbouring only *S aureus*. As all our titres were expressed as multiples of the upper limit of normal for appropriate ages the higher titres could not be explained by age Patients in groups A and B also had similar clinical scores (61 and 58), lung function, and forced expiratory volume in one second being 76% and 65%, respectively. *S aureus* in dual colonisation with *P aeruginosa* might therefore have an impact on the deterioration reported in patients, when *P aeruginosa* colonisation is established.[1–3] This might have important clinical implications as in our experience the colonising pattern seldom shifts abruptly from *S aureus* to *P aeruginosa*. Both pathogens coexist for a variable length of time, and this has to be taken into account when choosing the antibiotics.

The serum titres returned to normal in nearly 90% of the patients after antimicrobial treatment. Thus the present data suggest that measurement of antibodies to teichoic acid and alpha toxin may be useful in the treatment of infections in patients with cystic fibrosis who are colonised with *S aureus*, especially if they have low grade infections with normal haematological findings.

We thank Ms E Andersson, Ms E Norstrom and Ms I Olsson for technical assistance and Dr A-S Malmborg for bacteriological examination This work was supported by grants from the Swedish Association against Heart and Chest Disease, the Swedish National Association for Cystic Fibrosis, and the Karolinska Institutet

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## Thirty years ago

### Cyanotic attacks in newborn infants

*R S Illingworth (Sheffield)—Arch Dis Child* 1957;**32**:328–32

Paediatrics has been greatly enriched through the years by Professor Ronald Illingworth's careful clinical studies of the development and behaviour of infants and children, normal and abnormal. In this paper of 30 years ago he recorded his observations of cyanotic attacks in 170 newborn infants. Sixty per cent were premature The attacks began in the first 24 hours in 40% and in the first three days in 70% In 40% there was only a single attack, while 32% had two to four attacks and 28% five or more attacks In the mothers of the affected babies there was a significantly high incidence of toxaemia, hypertension, and antepartum haemorrhage Asphyxia neonatorum of some severity had been recorded in 24% of the babies Twitching or convulsions developed in 27 babies, but in only four of these was there twitching at the time of a cyanotic attack. The mortality in this series was 48% Mortality was 70% in premature babies compared with 15% in those born at full term. This corresponded with figures of 10·9% and 0·7%, respectively, in all other premature and term babies in the hospital. Fifty eight per cent of the babies who had one to four cyanotic attacks recovered compared with 32% of those who had five or more attacks Of the 27 infants with twitching or convulsions, 19 died The principal necropsy finding was severe atelectasis with or without hyaline membrane disease. The second commonest finding was gross cerebral haemorrhage (site not specified) Pronounced cerebral oedema was also noted

Illingworth discussed the difficulty in determining the cause of cyanotic attacks in the newborn He concluded that while some were due to respiratory obstruction from mucus, meconium, or vomitus, many were due to apnoea without respiratory obstruction The reasons for the apnoea could not be determined, but he noted a contemporary American observation that apnoea was mostly confined to babies in whom there had been a notable rise in respiratory rate after the first hour

**Comment.** It is easy to forget that in 1957 we knew very little about the pathophysiology of the respiratory distress syndrome or of the microanatomy and pathogenesis of intracranial bleeding and the effects on the cerebral blood vessels of sudden alterations in blood gas tensions The highly sophisticated diagnostic and therapeutic techniques that are routine in the intensive neonatal care units of today had still to be developed.

J H HUTCHISON

*Archives of Disease in Childhood,* 1987, **62,** 912–916

# Growth hormone in short, slowly growing children and those with Turner's syndrome

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SUMMARY Results of an aborted placebo controlled trial of treatment with human pituitary growth hormone in children with Turner's syndrome and short, slowly growing children are reported. One child in each group had a considerable reduction in growth rate standard deviation score while taking growth hormone. The remaining eight patients with Turner's syndrome and 10 short, slowly growing patients who received growth hormone showed mean rises in growth rate of greater than two standard deviation scores. Neither placebo group showed a mean increase in growth rate standard deviation score. These differences were significant.

Some short children who grow slowly and have normal serum concentrations of growth hormone during pharmacological provocation have been shown to increase their growth rate during treatment with growth hormone.[1] Girls with Turner's syndrome have also shown improved growth during short periods of treatment with the hormone.[2] Neither group of children has received growth hormone in a placebo controlled trial. Multicentre trials were therefore established and coordinated by the Health Services Human Growth Hormone Committee to find out if treatment with growth hormone could provoke a significant increase in their rates of growth.

## Patients and methods

Turner's syndrome was diagnosed from chromosomal analysis of peripheral blood lymphocytes. Short, slowly growing children were selected who had a height for chronological age at least 2·5 standard deviations below the mean and a growth rate below the 25th centile during the year before the trial. The standards for height and growth rate are those of Tanner *et al*.[3] Bone ages estimated by the TW2 system were either delayed or concordant with chronological age.[4] Children were excluded if they had been born prematurely (<37 weeks' gestation), had had a birth weight below the 3rd centile for gestational age, or showed definite dysmorphic features.

No child in either group had received previous hormonal treatment. All patients were prepubertal as defined by Tanner[5] and had normal endocrine function, except for some patients with Turner's syndrome who had raised gonadotrophin concentrations in serum. Each patient had achieved a growth hormone concentration greater than 15 mU/l on testing. Anthropometric measurements were recorded at the child's local growth centre at three monthly intervals for at least 12 months, or at about yearly intervals for at least three years before acceptance.

The trial design for both groups of patients was identical. Each child was allocated by a double blind random method to one of three groups, and the intended protocol was in three phases; group A were to receive growth hormone 4 IU thrice weekly by subcutaneous injection for 12 months; group B were to receive the same regimen of growth hormone for only six months, then placebo injections thrice weekly subcutaneously for six months; and group C were to receive placebo for six months then growth hormone for six months. All three groups were to be monitored for a further six months of no treatment.

The placebo was indistinguishable in appearance and presentation from growth hormone. Anthropometric measurements were performed at least every two months by the regular anthropometrist at each growth centre. Bone age was to be estimated at entry and six monthly thereafter.

Measurements of height and rate of growth are reported as standard deviation scores for age and sex according to Tanner *et al*.[3] Standard deviation scores for height and rate of growth for the patients with Turner's syndrome were derived from data in published series of girls with Turner's syndrome who had not received hormone treatment.[6 7] Rate of growth at entry was calculated from the preceding six months, or longer (maximum 1·3 years) when a recent measurement was not available. Consent was obtained from parents and any child over 12 years old.

Comparisons of the characteristics of the groups treated with growth hormone or placebo at entry into the trial and their respective standard deviation scores for growth rate were made by unpaired Student's *t* test or Fisher's exact test. Differences in growth rate standard deviation score within each group were analysed by paired Student's *t* test (one tailed or two tailed).

## Results

Thirty patients with Turner's syndrome and 50 short, slowly growing children entered the trial from September 1984 onwards. The trial was stopped when growth hormone was withdrawn from use in the United Kingdom in May 1985 after early reports of the development of Creutzfeldt-Jakob disease in patients treated with growth hormone in the United States and United Kingdom.[8] Fourteen patients with Turner's syndrome and 19 short, slowly growing children had completed 0·4 years or more of the first phase of the trial by that time. The results on these children from eight growth centres are presented (after exclusion of one boy in the short, slowly growing group taking growth hormone who progressed to pubertal stage 2, testicular volume 10 ml each side, after six months of the trial). The growth hormone group represents patients in groups A and B and the placebo group and those in group C of the original protocol. These patients had not all completed the first six months of the study, hence bone age data are incomplete.

### PATIENTS WITH TURNER'S SYNDROME

Seven subjects in the growth hormone group and one in the placebo group had a 45 XO karyotype, the remainder having chromosomal variants. This difference was not significant (Fisher's exact test). Table 1 outlines details of chronological age, height, growth rate standard deviation score at entry to the trial, and growth rate standard deviation score and bone age changes during treatment in the growth hormone and placebo groups. There were no significant differences at entry (Student's *t* test, two tailed) although the mean growth rate standard deviation score of the Turner's syndrome placebo group (+ 1·1) was different from that of the growth hormone group. As these patients were assessed according to standards for Turner's syndrome, their mean growth rate standard deviation scores at entry should not have differed from zero. This difference would have been less marked if the growth rate standard deviation score at entry had been obtained over at least a full year—growth hormone group growth rate standard deviation score mean (SD) − 0·8 (1·4); placebo group growth rate standard deviation score − 0·1 (1·0)—rather than six months, and the placebo group would not then have shown a significant fall in growth rate standard deviation score. The shorter interval was considered more appropriate for comparison with the six month period of treatment.

Figure 1 shows the individual changes in growth rate standard deviation score during the treatment period. Eight subjects receiving growth hormone showed an increase in growth rate standard deviation score (range + 0·1 to + 5·5, or growth rate − 0·2 to + 4·5 cm/year). The ninth subject had a reduction of 3·6. The mean increment in growth rate standard deviation score of 1·7 for the group was significant ($p < 0.05$, one tailed). Four girls receiving placebo showed a fall in growth rate standard deviation score (range − 1·4 to − 3·1), the fifth having a marginal reduction of 0·05 (group

Table 1 *Patients with Turner's syndrome: chronological age, height, and growth rate at entry to trial and during trial*

| | *Growth hormone group (n = 9)* | | *Placebo group (n = 5)* | |
|---|---|---|---|---|
| | *Mean (SD)* | *Range* | *Mean (SD)* | *Range* |
| Chronological age (years) | 9·81 (2·78) | 4·42 to 13·35 | 10·22 (2·74) | 4·13 to 14·45 |
| Height (cm) | 116·3 (12·0) | 92·4 to 133·3 | 113·5 (17·4) | 85·1 to 132·4 |
| Height standard deviation score for chronological age | − 0·3 (0·7) | − 1·0 to + 1·0 | − 0·9 (0·7) | − 1·8 to − 0·2 |
| Trial period (years) | 0·49 (0·02) | 0·46 to 0·54 | 0·48 (0·04) | 0·42 to 0·52 |
| Growth rate at entry (standard deviation score) | − 0·3 (1·4) | − 2·4 to + 1·6 | 1·1 (1·0) | − 0·4 to + 2·4 |
| Growth rate on treatment (standard deviation score) | 1·4 (1·8) | − 2·0 to + 3·3 | − 0·7 (1·8) | − 2·0 to + 2·4 |
| *Bone age advancement | 1·0† (0·6) | 0·2 to 1·7 | 1·5‡ (1·1) | 0·8 to 2·7 |

*Bone age advancement = change in bone age/change in chronological age, †n = 6, ‡n = 3

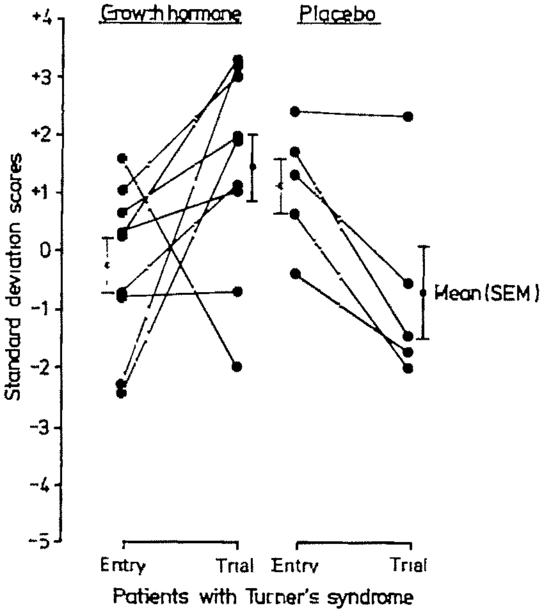

Fig. 1 *Children with Turner's syndrome growth rate scores at entry and during trial.*

range −0·2 to −2·8 cm/year). The mean change of − 1·8 with placebo was a significant fall (p < 0·05, two tailed). Thus the mean increase in growth rate score during treatment with growth hormone was significantly different from the response of the placebo group (p < 0·025 one tailed).

The girl whose score changed by − 3·6 differed significantly from the rest of her group. When she was excluded from the analysis both the mean change in growth rate standard deviation score (+ 2·4) in the remainder of the growth hormone group and the difference in response from the placebo group reached greater significance (p < 0·005, two tailed, and < 0·005, one tailed, respectively).

Bone age at entry ranged from 3 to 12 'years' in both groups. The mean change in bone age during treatment with growth hormone was not inappropriate, but little can be inferred from such a short study period.

### SHORT, SLOWLY GROWING CHILDREN

Table 2 outlines details of chronological age, height, growth rate standard deviation score at entry, and growth rate standard deviation score and changes in bone age during treatment of the growth hormone and placebo groups.

The mean age of the placebo group (11·1 years) was significantly higher (p < 0·05, two tailed) than that of the growth hormone group (7·6 years), which contained four children under 6 years old. Bone age ranged from 7·6 to 9·8 'years' in the placebo group and from 2·0 to 11·1 'years' in the growth hormone group. The mean heights of the two groups were significantly different (p < 0·05, two tailed). Although initially selected for having a low growth rate (below the 25th centile) over one year before acceptance three children in each group had a higher growth rate than this by the time of entry. In turn, three children (two in the growth hormone group) had grown so well that they were no longer as short as 2·5 standard deviations below the mean for their height. The use of growth rate standard deviation score over the nearest whole year to entry (growth hormone group mean − 1·1, placebo group mean − 1·3) would not have significantly affected the following statistical analysis.

Figure 2 shows individual changes in growth rate standard deviation score during the treatment period. Nine of the growth hormone group showed an increase in growth rate standard deviation score

Table 2 *Short, slowly growing children chronological age, height, and growth rate at entry to trial and during trial*

| | *Growth hormone group (n = 11· 9 boys, 2 girls)* | | *Placebo group (n = 7 5 boys, 2 girls)* | |
|---|---|---|---|---|
| | *Mean (SD)* | *Range* | *Mean (SD)* | *Range* |
| Chronological age (years) | 7·63 (3·25) | 2·64 to 12·70 | 11·10 (1·08) | 10·00 to 13·15 |
| Height (cm | 105·3 (15·7) | 79·3 to 129·3 | 119·6 (5·0) | 114·1 to 126·7 |
| Height standard deviation score for chronological age | − 3·1 (0·7) | − 2·2 to − 4·3 | − 3·5 (0·6) | − 2·4 to − 4·4 |
| Trial period (years) | 0·49 (0·04) | 0·40 to 0·54 | 0·48 (0·03) | 0·42 to 0·52 |
| Growth rate at entry (standard deviation score) | − 1·1 (1·4) | − 3·5 to + 1·5 | − 0·9 (1·1) | − 2·5 to + 0·6 |
| Growth rate on treatment (standard deviation score) | 0·3 (2·0) | − 4·0 to + 3·0 | − 0·9 (1·2) | − 2·3 to + 1·3 |
| *Bone age advancement | 0·9† (0·5) | 0·2 to 1·6 | 1·6‡ (1·4) | 0·6 to 3·6 |

*Bone age advancement = change in bone age/change in chronological age; †n = 9, ‡n = 4

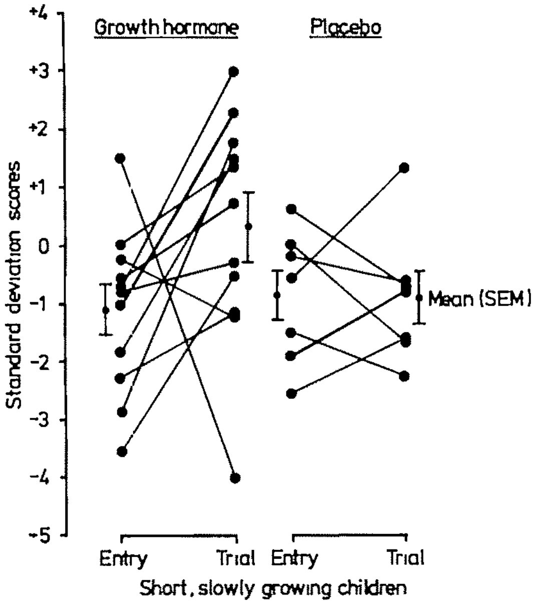

Fig. 2 *Short, slowly growing children growth rate scores at entry and during trial*

(range + 0·5 to + 4·6, or growth rate + 1·1 to + 3·5 cm/year), with two patients showing a decrease (− 1·0 and −5·5, or − 1·9 and − 4·4 cm/year), the mean change in score of + 1·4 not reaching significance at the 5% level. Three children in the placebo group showed moderate increases and four showed decreases during treatment (− 1·7 to + 1·9; or − 1·6 to + 1·4 cm/year). There was no change in the mean growth rate standard deviation score for this group. Thus the mean response from all subjects receiving growth hormone was not significantly different from that of the placebo group ($p > 0{\cdot}05$, one tailed). As occurred with the group with Turner's syndrome, however, the child with the highest entry score to receive growth hormone had a response (− 5·5) significantly different from that of the remainder of the group and could be considered separately. His growth rate over 1·8 years had averaged the 25th centile with a period of above average growth immediately before entry. When his response was excluded the remainder of the growth hormone group showed a mean rise of + 2·1 ($p < 0{\cdot}005$, one tailed) which was significantly different from the mean placebo response ($p < 0{\cdot}025$, one tailed).

## Discussion

There was great disappointment among clinicians, parents, and children when these trials were halted prematurely. Important ethical issues were entailed to determine which further groups of children might benefit from treatment with growth hormone and whether it was justifiable to have a control group receiving placebo by a parenteral route. Some growth centres were unable to admit children to the study because local ethical committees refused to approve the use of a placebo controlled group. Nevertheless, recruitment was good owing to the enthusiasm of families attending other growth centres. Possible placebo effects on growth of an injection regimen such as that in this study have never to our knowledge been reported before Inclusion of a placebo control group may improve the validity of using six month phases to reduce the length of a trial such as this. The potential unreliability of a six month measurement of growth rate rather than a whole year is recognised, and our results may reflect the tendency for regression to the mean over shorter intervals. Seasonal fluctuation may account for the − 3·6 change in growth rate score observed for one subject in the Turner's syndrome growth hormone group. Her subsequent six monthly measurements without treatment showed swings of similar magnitude about the mean.

This trial was abandoned for reasons unconnected with its objectives.[8] Statistical analysis of the limited unselected data thus remains valid. The findings provide further encouraging evidence that patients with Turner's syndrome might respond to treatment with growth hormone for six months or longer. The short, slowly growing children receiving growth hormone showed, with the exception of one boy, a significant mean rise in growth rate standard deviation score. This group of children is likely to be heterogeneous,[1] and other studies are clearly essential to determine which children could benefit from treatment with growth hormone. A growth rate below the 25th centile may not be helpful in selecting children for study: a higher centile would exclude children exhibiting catch up growth at the time of entry

An important finding was the absence of an increase in the mean growth rate standard deviation score of either placebo group The availability of biosynthetic growth hormone now permits the further trials that are necessary to establish how treatment with growth hormone might be of short or long term benefit to children with Turner's syndrome and those of short stature with normal growth hormone concentrations as defined by conventional criteria.

We thank the directors of the regional growth centres and their patients for their cooperation in the trials

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# Human milk and preterm formula compared for effects on growth and metabolism

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SUMMARY Metabolic tolerance to a 'premature formula' feed was studied in a group of small immature infants, mean (SD) gestation 27·8 (1·4) weeks. Ten infants weighing 880–1295 g at the time of the study were fed on SMA low birthweight formula for a mean (SD) of 23·5 (5·5) days and were compared with 10 who were fed on expressed breast milk for 25·8 (6·1) days. The infants were well matched for weight, gestation, and postnatal age at the time of the study and were receiving full enteral feeds. They were investigated by balance techniques and plasma sampling on at least two occasions. Ten larger infants weighing 1330–1740 g and being fed on the same formula feed were also studied as an additional control group. Formula fed infants retained more nitrogen and gained weight faster. Plasma phosphorus concentrations were higher in the group fed on the formula feed, and alkaline phosphatase activity was lower. There were no significant differences in plasma concentrations of urea, electrolytes, or albumin or in acid base status. Taurine and arginine concentrations were higher in the group being breast fed, but there were no other significant differences in plasma amino acids, and no toxic concentrations occurred after either feed. The results of this study show that this formula (and presumably other feeds of similar composition) seem to be metabolically safe for the smallest infants.

Preterm formula feeds have been in use in neonatal nurseries for some years, and there have been several reports assessing their effects on growth and metabolism. The smallest infants are vulnerable to the harmful effects of unsuitable feeding—for example, poor gastric emptying, milk bolus obstruction,[1] metabolic acidosis,[2] hypertyrosinaemia,[3] and even necrotising enterocolitis.[4] Nevertheless, data evaluating the effects of preterm formula feeds on these tiny infants are scanty and there is a reasonable reluctance, especially among neonatal nurses, to substitute such feeds for breast milk despite the known nutritional disadvantages of breast milk for such babies; these include appreciable deficiencies in protein, sodium, calcium, and phosphorus.[5–7] This paper reports an investigation into growth and metabolism in extremely immature infants who weighed <1300 g on entry to the study, in which a preterm formula feed (SMA low birthweight formula) was compared with expressed breast milk.

## Patients and methods

**Infants.** Thirty seven infants were recruited into the study, but this analysis describes 20 infants matched for weight, gestation, and postnatal age. Ten were fed the formula feed and 10 expressed breast milk (EBM); a further 10 larger infants fed on formula feed acted as an additional control group It was planned that the low weight infants should all weigh <1250 g at the time of the study, but because of the continued need for intravenous hydration in some, the design was modified to include infants between 1250 and 1300 g as well. Because infants suitable for such a study are rarely available in large numbers the final number studied was dictated by constraints of time and money rather than by formal examination of the power of the study to discriminate between the groups in respect of the variables associated with outcome. We attached special importance to obtaining enough infants to allow proper matching of weight, age, and gestation in two feeding groups of reasonable size. All suitable infants admitted to the neonatal unit at this hospital during the period of study were recruited, providing their parents agreed. Criteria of suitability were that there was no major malformation, no need for continued ventilation or intravenous feeding, and no important additional factors present (such as a patent ductus arteriosus or major intraventricular haemorrhage) that might limit growth. Infants were nursed in thermoneutrality, and none received theophyllines during the period of the study.

**Feeding.** Initial enteral feeding was with breast milk (either maternal or banked EBM). and the infants entered the study when they tolerated 180 ml/kg/day. At this time infants whose mothers wanted to continue providing breast milk were allocated to remain on EBM and formed the breast milk control group. Infants whose mothers did not wish to provide milk were allocated to the formula group Because of the high rate of breast feeding at this hospital 27 infants fed on breast milk were recruited before 10 could be recruited to be fed on the formula. Table 1 gives details of these 10 and of the 10 with whom they were matched who were fed with EBM. Ten larger infants (weighing 1330–1740 g at the start of the study) were also fed with SMA formula feed to serve as a control for the group weighing <1300 g when the various metabolic criteria were investigated: Table 2 gives details of these babies. The EBM group received fresh maternal breast milk supplemented as necessary with pasteurised banked breast milk (usually ≤25%) and with sodium chloride (to maintain plasma sodium concentrations above 130 mmol/l), phosphorus (25 mg as buffered sodium phosphate daily), calcium (65 mg as calcium lactate/gluconate daily), and vitamin D (600 IU daily). The formula fed group received no other form of nutrition except supplementary vitamin D. Table 3 gives the macronutrient composition of SMA low birthweight formula together with the protein and energy content of the EBM.

The mean (SD) length of the study period for the formula fed group was 23·5 (5·5) days and for the EBM group 25·8 (6·1) days. The study was approved by the hospital ethical committee.

**Measurements of growth.** All infants were weighed daily on a calibrated Marsden spring balance (Marsden Weighing Machines, London W9) accurate to within 5 g. Crown-heel length was measured twice a week to the next succeeding 1·0 mm on a neonatal

Table 1 *Details of infants studied weighing <1300 g*

| *Case No* | *Birth weight (g)* | | *Gestation (weeks)* | | *Age at start of study (days)* | | *Weight at start of study (g)* | |
|---|---|---|---|---|---|---|---|---|
| | *SMA* | *EBM* | *SMA* | *EBM* | *SMA* | *EBM* | *SMA* | *EBM* |
| 1 | 1170 | 1200 | 28 | 27 | 14 | 20 | 1180 | 1170 |
| 2 | 1010 | 990 | 27 | 28 | 35 | 25 | 1200 | 1140 |
| 3 | 950 | 950 | 25 | 26 | 22 | 16 | 990 | 955 |
| 4 | 1175 | 1000 | 30 | 29 | 12 | 22 | 1290 | 1280 |
| 5 | 900 | 900 | 28 | 29 | 12 | 10 | 880 | 890 |
| 6 | 970 | 890 | 27 | 27 | 27 | 29 | 1160 | 1050 |
| 7 | 1100 | 1150 | 27 | 28 | 15 | 10 | 1190 | 1070 |
| 8 | 890 | 880 | 25 | 29 | 12 | 12 | 880 | 910 |
| 9 | 1330 | 1250 | 29 | 30 | 12 | 12 | 1270 | 1290 |
| 10 | 1140 | 850 | 25 | 26 | 26 | 40 | 1295 | 1300 |
| Mean | 1064 | 1019 | 27 8 | 27 9 | 19 | 20 | 1134 | 1106 |
| SD | 143 | 149 | 1 4 | 1 4 | 8 | 10 | 159 | 156 |

Table 2 *Details of infants studied weighing ≥1300 g fed on formula feed*

| *Case No* | *Birth weight (g)* | *Gestation (weeks)* | *Age at start of study (days)* | *Weight at start of study (g)* |
|---|---|---|---|---|
| 1 | 8[illegible]0 | 26 | 44 | 1330 |
| 2 | 12[illegible]0 | 28 | 27 | 1400 |
| 3 | 14[illegible]0 | 30 | 14 | 1400 |
| 4 | 15[illegible]0 | 30 | 5 | 1410 |
| 5 | 13[illegible] | 31 | 12 | 1510 |
| 6 | 13[illegible] | 32 | 11 | 1550 |
| 7 | 11[illegible] | 26 | 37 | 1550 |
| 8 | 13[illegible] | 31 | 15 | 1560 |
| 9 | 9[illegible] | 26 | 47 | 1710 |
| 10 | 14[illegible] | 29 | 25 | 1740 |
| Mean | 12[illegible]1 | 28 9 | 24 | 1516 |
| SD | 2[illegible]7 | 2 3 | 15 | 135 |

Table 3 *Composition of feeds (constituents per litre)*

| | *SMA low birthweight formula** | *EBM* |
|---|---|---|
| Mean (SD) energy (kJ) | 3344 | 3118 (38)† |
| Mean (SD) protein (g) | 20 | 13 7 (0 3) |
| Whey casein | 60 40 | |
| Fat‡ (g) | 44 | NM |
| Carbohydrate (g) | | |
| Lactose | 43 | NM |
| Maltodextrin | 43 | |
| Sodium (mg) | 320 | NM |
| Potassium (mg) | 750 | NM |
| Chloride (mg) | 530 | NM |
| Calcium (mg) | 750 | NM |
| Phosphorus (mg) | 400 | NM |
| Zinc (mg) | 5 | NM |
| Copper (mg) | 0 7 | NM |
| Osmolality (mmol/kg) | 268 | NM |

*Manufacturer's data †Gross energy ‡Beef fat, vegetable oils, 10% medium chain triglyceride NM Not measured

stadiometer. Occipitofrontal head circumference and mid-upper arm circumference were measured twice a week to the next succeeding 1·0 mm with a paper tape measure. Upper arm and lower leg lengths were also measured twice a week to the next succeeding 1·0 mm with a caliper.[8] Triceps and subscapular skinfold thicknesses were measured twice a week to the next succeeding 0·1 mm with a Harpenden caliper.[9] All anthropometric measurements except weight were done by the same trained person (OO), whose variation in multiple determinations did not exceed 5% of the mean for any measurement.

**Measurement of feeds.** All feeds were given by nasogastric tube Volume of intake was measured and carefully recorded for each infant During balances all regurgitations were collected on preweighed pads and their weight, converted to volume, was subtracted from the intake.

**Measurement of balances.** Two energy and nitrogen balances were performed for each infant, separated by one to two weeks. Before and after the balances, which lasted three days, a carmine marker was given. All stools passed between the markers were collected in napkin liners[10] and immediately frozen at −24°C. They were later weighed, freeze dried, weighed again, homogenised, and analysed for energy by bomb calorimetry,[11] for fat by the gravimetric technique, using the Soxtec apparatus, and for nitrogen by the Kjeldahl technique, using the Kjeltec apparatus. The Soxtec and Kjeltec systems were devised by Tecator AB, Box 70, S-263 01, Höganas, Sweden, and based on the Soxhlet gravimetric fat assay and Kjeldahl nitrogen assay Urine was collected in preweighed, disposable nappies free of nitrogen,[10] sealed in plastic bags at each nappy change, and immediately frozen at −24°C. The nappies were later reweighed to obtain urine volume and then washed in a known volume of water. After filtering, aliquots were freeze dried and analysed for energy and nitrogen. During one of the three day balance periods urine was collected for 24 hours on ice by continuous aspiration using a perineal bag and a small electric pump [12] This urine was also analysed for nitrogen and energy All analyses were done without knowing which type of feed the infant was having.

Representative samples of breast milk and a single sample of formula (which had a constant composition) were analysed for energy and nitrogen, and these values were used in the balance calculations.

**Biochemical measurements.** Weekly measurements were made of plasma concentrations of urea, sodium, potassium, bicarbonate, calcium, and phosphorus with an autoanalyser. Alkaline phosphatase activity and plasma amino acid concentrations were measured fortnightly with an LKB 4400 amino acid analyser (LKB Biochrom Ltd, Cambridge Science Park, Cambridge, England). Blood gas tensions were measured weekly from a capillary sample.

**Statistical analysis.** All data were normally distributed, and the significance of the differences was calculated with Student's *t* test.

## Results

**Infants <1300 g: SMA low birthweight formula feed *v* EBM.** Tables 1 and 2 show that the groups were comparable for birth weight, gestation, and age and weight at the time of the study.

*Feed intake*

Intake during the two balance periods (total six days) was representative of the overall intake during the study period. Infants receiving SMA low birthweight formula feed received a mean (SD) of 606 (105) kJ/kg daily and 598 (85) mg nitrogen/kg. Infants receiving EBM received 602 (134) kJ/kg, and 424 (97) mg nitrogen/kg. Table 3 gives the protein and energy contents of the EBM.

*Macronutrient digestion and retention*

Table 4 gives the data for energy and protein digestibility and retention Digestibility is defined as energy or nitrogen intake minus faecal energy or nitrogen losses×100 (%) energy or nitrogen intake. Retention is defined as digestible energy or nitrogen (kJ or mg/kg) minus urinary losses of energy or

Table 4 *Mean (SD) macronutrient digestion and retention*

| | *EBM* | | *SMA low birthweight formula feed* | | |
|---|---|---|---|---|---|
| | *Infants <1300 g* | | *Infants <1300 g* | | *Infants ≥1300 g* |
| Energy digestibility (%) | 77·3 ([illegible]·5) | NS | 78·5 (5·4) | NS | 81·0 (6·0) |
| Protein digestibility (%) | 86·1 ([illegible]·9) | $t$=2·1<br>p=0·04 | 81·6 (4·8) | $t$=2·5<br>p=0·02 | 86·2 (3·1) |
| Metabolisable energy (kJ/kg/day) | 427 ([illegible]) | NS | 490 (80) | NS | 494 (54) |
| Nitrogen retention (mg/kg/day) | 221 ([illegible]) | $t$=3·0<br>p=0·006 | 337 (114) | NS | 404 (62) |

nitrogen (kJ or mg/kg), expressed as a daily retention rate in kJ or mg/kg.

Protein digestibility was greater (p=0·04) in babies fed on breast milk than in those fed on the formula feed, but nitrogen retention was considerably greater (p=0·006) in those fed the formula feed. No significant difference in metabolisable energy intake was found between the two groups, but the mean in the formula group was 63 kJ/kg/day greater than the mean in the group fed on breast milk.

### *Growth*

Table 5 shows a comparison of the data about growth. Weight gain was significantly greater in the formula fed infants (p=0·003) with the difference averaging nearly 9 g/kg/day. Growth of the subscapular fat fold was also significantly greater in the formula fed group (p=0·02). The growth rates of triceps fat fold and mid-upper arm circumference did not differ between the groups.

No significant differences were found in linear growth or head size between the two groups

### *Metabolism*

Table 6 shows the results of the measurements of plasma pH, base excess, concentrations of urea, electrolytes, albumin, calcium, and phosphorus, and

Table 5 *Mean (SD) anthropometric measurements during growth in infants fed on EBM and formula*

| | *EBM <1300 g* | *Significance of difference* | *SMA low birthweight formula feed* | |
|---|---|---|---|---|
| | | | *<1300 g* | *≥1300 g* |
| Weight gain (g/kg/day) | 13·6 (3·6) | $t$=3·5<br>p=0·003 | 22·1 (6·3) | 17·3 (3·1) |
| Length gain (mm/day) | | | | |
| Crown-heel | 1·2[illegible] (0·52) | NS | 1·02 (0·54) | 1·70 (0·22) |
| Upper arm | 0·2[illegible] (0·16) | NS | 0·36 (0·19) | 0·38 (0·18) |
| Lower leg | 0·3[illegible] (0·12) | NS | 0·40 (0·25) | 0·42 (0·19) |
| Circumferential growth (mm/day) | | | | |
| Head | 1·4[illegible] (0·18) | NS | 1·97 (0·77) | 1·31 (0·74) |
| Mid-upper arm | 0·6[illegible] (0·23) | NS | 0·58 (0·23) | 0·61 (0·22) |
| Fat fold measurements (mm/week) | | | | |
| Triceps | 0·1[illegible] (0·30) | NS | 0·46 (0·36) | 0·32 (0·29) |
| Subscapular | 0·1[illegible] (0·21) | $t$=2·4<br>p=0·02 | 0·39 (0·15) | 0·31 (0·25) |

Table 6 *Mean (SD) of biochemical measurements*

| | *EBM <1300 g* | *Significance of difference* | *SMA low birthweight formula feed* | |
|---|---|---|---|---|
| | | | *<1300 g* | *≥1300 g* |
| Urea (mmol/l) | 1·85 (0·92) | NS | 1·58 (0·87) | 1·81 (1·02) |
| Sodium (mmol/l) | 136·3 (5·[illegible]) | NS | 134·6 (3·6) | 138·1 (3·7) |
| Potassium (mmol/l) | 5·07 (1·13) | NS | 4·91 (0·90) | 5·20 (0·71) |
| Albumin (g/l) | 30 (3) | NS | 32 (8) | 33 (7) |
| Calcium (mmol/l) | 2·62 (0·23) | NS | 2·29 (0·21) | 2·22 (0·12) |
| Phosphorus (mmol/l) | 1·56 (0·43) | $t$=2·9<br>p=0·01 | 2·15 (0·44) | 1·87 (0·42) |
| Alkaline phosphatase (IU/l) | 504 (241) | $t$=2·2<br>p=0·036 | 331 (107) | 431 (140) |
| pH of capillary blood | 7·31 | NS | 7·28 | 7·30 |
| Base excess (mmol) | −4 | | −5 | −4 |

alkaline phosphatase activity made after two weeks in the two groups The only significantly different findings were a lower plasma phosphorus concentration in the breast fed group ($p<0\cdot01$) and higher alkaline phosphatase activity ($p=0\cdot036$).

The figure shows the results of estimations of amino acid concentrations in plasma. In formula fed infants taurine and arginine concentrations were lower than those in the breast fed group ($p<0\cdot05$), but there were no other significant differences. Table 7 shows the highest measured concentrations of certain selected amino acids which may be potentially toxic. In the formula fed group the highest values were all from one infant (birth weight 970 g, age at sampling 14 days). In the EBM group the highest values were found in three different infants.

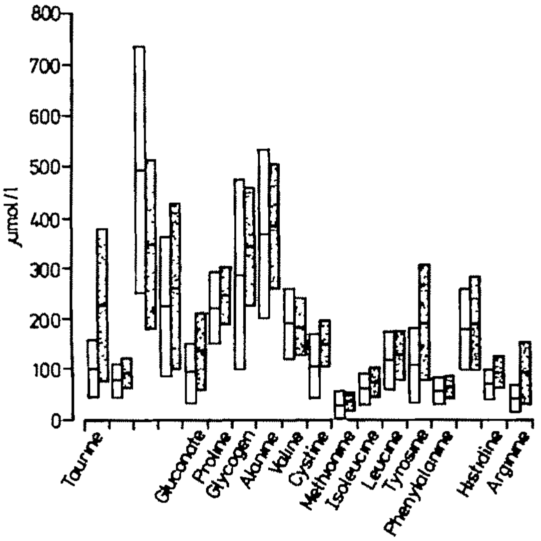

Figure *Plasma aminogram in formula fed infants* □□ *and those fed on breast milk* ▨. *Values are means (SD).*

Table 7 *Highest measured concentrations of selected amino acids in infants weighing <1300 g fed EBM and SMA low birthweight formula (µmol/l)*

| *Amino acids* | *EBM* | *SMA low birthweight formula feed* |
|---|---|---|
| Methionine | 70 | 88 |
| Tyrosine | 393 | 258 |
| Phenylalanine | 105 | 115 |
| Histidine | 160 | 130 |
| Proline | 313 | 328 |
| Valine | 290 | 323 |
| Leucine | 230 | 210 |
| Isoleucine | 123 | 105 |

**Infants ≥1300 g fed on SMA low birthweight formula.** Tables 4–6 show details of food intake, digestibility, growth rates, and biochemical variables in the larger infants. These infants digested protein more easily ($p=0\cdot02$), but retention of nitrogen, and amount of energy metabolised were not significantly different from those in the other groups. The larger infants gained marginally less weight (17·3 v 22·1 g/kg/day), but there were no substantial differences in the biochemical variables with the exception of the amino acids; concentrations of hydroxyproline, glycine, and arginine were all significantly higher in the larger babies ($p<0\cdot05$). Although no significant difference was found for any other amino acid, the mean value for every amino acid except taurine was higher in the larger than the smaller infants. When all amino acids were considered together the mean value was significantly greater in the larger babies ($p<0\cdot01$).

## Discussion

Concern over the metabolic consequences of feeding a relatively high protein intake to preterm infants has not been borne out by the results of this study.[2 13] Even the smallest infants receiving premature formula feed achieved plasma concentrations of potentially toxic amino acids that were well within the limits of probable safety[14] and were no higher than those reached by those fed on breast milk.[14] The importance of differences in plasma amino acid concentrations between infants of such immaturity is not yet known. It would be of concern if the branched chain amino acids were particularly low in any feed given to an infant who should be growing, because this pattern is one of the features of kwashiorkor,[15] but this was not the case in any of the infants in our study. It would also be of concern if any infant showed abnormally high concentrations of those amino acids that may be toxic, but this was not the case either. and there were no significant differences in pH, base excess, or blood urea concentration to suggest that the formula fed infants were in metabolic difficulty compared with the breast fed infants.

The lack of important differences between the two groups in these respects may reflect the relatively high protein concentrations that are achieved in preterm breast milk,[6 16–18] although we cannot confirm this because we did not monitor the protein content of our EBM throughout the study. A formula consisting mainly of whey, however, with a protein concentration of about 2·0 g/100 ml would be unlikely to cause toxic effects due to inadequate protein metabolism in infants as small as 900 g, provided they were growing. This proviso is important because the ill or poorly growing infant who is unwell may be unable to use dietary proteins adequately, and there is no guarantee that under such conditions potentially dangerous metabolic effects will not occur. It is also unwise to increase the volume of enteral feed in the immature infant until tolerance is adequate and the infant is growing.

We did not expect the larger infants to have higher concentrations of amino acids than the smaller. Examination of the data showed a higher mean feed intake in the larger infants together with greater net nitrogen retention, and this probably accounted for the differences in the concentrations of amino acids.

Arginine and taurine concentrations were lower in formula fed infants. There is no clinical disadvantage in having low plasma concentrations of arginine, though arginine synthetase activity is reduced in the fetus and low plasma concentrations might indicate deficiency [19] Arginine may protect the low birthweight infant from high dietary amino acid loads, perhaps through increased turnover in the urea cycle so there is a theoretical reason for suggesting that the intake of arginine should be greater than that provided by present formulas.[20] Taurine is an important constituent of bile salts in infants fed on human milk, and when formulas based on cows' milk (which are low in taurine) are used the bile acids are predominantly conjugated by glycine. This has given rise to concern that function of bile salts might be impaired when feeds low in taurine are used, but supplementation of such feeds with taurine has no effect on fat absorption in preterm infants [21] Taurine is an essential nutrient, and the prolonged use of diets lacking in taurine causes retinal damage in cats.[22] The amount of taurine required in the diet to prevent such abnormalities is certainly very small, and no lesions suggestive of taurine deficiency have ever been described to our knowledge in preterm or full term infants fed on formulas based on cows' milk All the infants in our study who were fed on the formula had measurable concentrations of taurine in the plasma, so it seems unlikely that it is necessary to supplement such formulas with taurine. A larger series of analyses of amino acid concentrations in the plasma of infants of low birthweight fed on the same formula failed to show significant differences in arginine or taurine when compared with a group fed on breast milk, though there were significant differences in concentrations of other amino acids.[23]

The data on calcium and phosphorus concentrations lend support to the view that breast milk is an inadequate source of phosphorus and should be supplemented.[7] [24-26] The higher phosphorus content of the preterm formula feed ensures a normal plasma phosphorus concentration in most infants and significantly lower alkaline phosphatase activity. Metabolic bone disease of prematurity is seen less commonly in infants fed on preterm formula feeds, and later linear growth is better.[7] The immature and rapidly growing infant needs a lot of phosphorus; adequate calcium retention will not occur without it, and in severe phosphorus depletion all the cellular mechanisms that produce energy will be impaired.[27-29]

The results of the balances confirm that a well designed formula feed achieves adequate macronutrient digestibility: there was no significant difference between the formula feed and breast milk in energy absorption and only a small reduction in protein absorption Nitrogen retention and mean metabolisable energy intake were higher in those babies fed on the formula, and this was reflected in their greater weight gain We were unable to show significant increases in linear growth or head growth in the formula fed group in this study, but six out of eight anthropometric measurements showed a greater mean increment in the formula fed group. Differences in linear growth are difficult to establish in very small infants owing to the high variability in measurements and the small absolute increments in growth Although worries have been expressed about the quality of weight gained by extremely low weight infants receiving premature formula feeds, in that more fat is deposited than in infants fed breast milk, there seems little doubt that there is an overall increase in growth in comparison with that seen with other types of feeding. Moreover, it is a physiological characteristic of the newborn infant to deposit fat reserves if given adequate dietary energy.

We conclude that it is probably safe to feed the growing preterm infant of extremely low weight (900–1300 g) on a preterm formula feed given in volumes that will result in a protein intake of not more than 4 g/kg/day. We do not know whether it is wise to begin using such formulas in the early days, but perhaps it is prudent to start enteral feeding with a feed of relatively low nutrient density Undigested food residues may well be important in the pathogenesis of necrotising enterocolitis, and gastric emptying in preterm infants is considerably slower when they are fed on formulas high in protein than when they are fed on expressed breast milk. It seems sensible, therefore, to begin enteral feeding in the smallest infants with breast milk and to introduce a premature formula feed only when the infant has established reliable gastric emptying and has begun to gain weight

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# Effect of diazoxide or glucagon on hepatic glucose production rate during extreme neonatal hypoglycaemia

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SUMMARY The relation between hepatic glucose production rate (HGPR) and plasma concentrations of insulin and glucagon was investigated in four term neonates who had severe hypoglycaemia. The hepatic glucose production rate was less than 20% of normal for fasting term neonates in all four babies and yet insulin concentrations were never $>12$ μU/ml; two babies had very low glucagon concentrations ($<60$ ng/l). Two further neonates with similar histories also had plasma glucagon concentrations that were also extremely low ($<20$ ng/l). A single intravenous bolus of glucagon caused a rapid rise in hepatic glucose production rate towards the normal range, which was sustained for many hours after the bolus had been given. Diazoxide given to one baby suppressed previously 'normal' insulin concentrations still further (4·2 to $<1·6$ μU/ml) and thereby restored the hepatic glucose production rate to normal. In view of the normal plasma insulin concentrations at a time when the hepatic glucose production rate was reduced, we feel that the absolute concentration of insulin may be less important than the insulin/glucagon molar ratio in the control of glucose homeostasis in this group of infants. The changing of this ratio by means of boluses of glucagon may be useful in preventing rebound hypoglycaemia, which so often occurs when dextrose infusions are reduced either accidentally or in an attempt to restart oral feeds.

Although hypoglycaemia is a well recognised complication in babies who are preterm or small for gestational age, it can also occur in term neonates who are otherwise well. In these babies it is often a severe problem in terms of clinical management. Many of them have no obvious disorder such as an inherited metabolic disease or maternal diabetes mellitus to explain their low plasma glucose concentration and yet they often require more than 55 μmol/kg/min of intravenous dextrose to prevent hypoglycaemia (normal range 27–44 μmol/kg/min). This extremely high rate of dextrose infusion sets this group of infants apart from others with hypoglycaemia because of their inability to maintain euglycaemia during even the shortest of fasts or during 'normal' rates of glucose infusion

They may still have an extremely labile plasma glucose concentration, despite being given dextrose intravenously, and often have convulsions if the rate of infusion falls suddenly, which may occur when the drip tissues. It is often assumed that the hypoglycaemia is due to 'hyperinsulinism',[1] but the exact relation between plasma insulin concentration and rate of glucose production and release from the liver remains unclear.

This relation has been studied in six infants (table 1). We have made serial measurements of the plasma concentration of insulin and glucagon in five infants, and in three we were able to measure the change in hepatic glucose production rate in response to treatment with diazoxide or glucagon.

## Patients

**Case 1.** A girl, the second of HLA identical twins, was born at term with birth weight 2640 g by elective lower segment caesarean section to unrelated Jewish parents. She required resuscitation at birth (Apgar scores 3 and 7 at one and five minutes, respectively) and by 10 hours had a plasma glucose concentration

Table 1 *Clinical data on the study group*

| *Case No* | *Birth weight (g)* | *At diagnosis* | | *Highest observed insulin concentration* | *Glucose concentration at this time* | *Pretreatment glucagon concentration (ng/l)* | *Treatment* |
|---|---|---|---|---|---|---|---|
| | | *Age (h)* | *Glucose concentration (mmol/l)* | | | | |
| 1 | 2640 | 10 | 0 | 11·8 | 2·4 | — | Diazoxide |
| 2 | 3000 | 50 | 0·6 | 10 | 0·6 | <60 | Glucagon |
| 3 | 2600 | 12 | 1 | 10 | 1 | — | Glucagon |
| 4 | 3200 | 46 | 0·2 | 90* | 2·5 | <60 | Glucagon |
| 5 | 2100 | 12 | 0 | 4 | 0 | <20 | Glucagon |
| 6 | 3900 | 1 | 0·1 | 9 | 2·6 | <20 | Glucagon |

*This baby had received boluses of 20% dextrose before the sample was taken

of 1 mmol/l, which failed to rise above 3 mmol/l over the next six days, even though she was given up to 83 µmol/kg/min of intravenous dextrose Glucose turnover measurements were made on day 6 and again after five days of treatment with oral diazoxide (10 mg three times a day). The first twin did not become hypoglycaemic at any stage.

**Case 2.** An Asian boy was born at term with birth weight 3000 g by elective lower segment caesarean section for breech presentation after an unremarkable pregnancy. Severe maternal bleeding occurred at delivery and he required resuscitation (Apgar scores 5 and 9 at one and five minutes, respectively). He fed poorly for the first two days and had a grand mal convulsion at 50 hours, at which time his plasma glucose concentration was 0·6 mmol/l. This failed to rise above 2 mmol/l, even though he was given up to 83 µmol/kg/min of intravenous dextrose for the next 24 hours. There was no evidence of sepsis and he was treated with phenobarbitone for the convulsions. Glucose turnover studies were performed during treatment with 200 µg/kg of intravenous glucagon on the third day of life.

**Case 3.** A boy was born at term with birth weight 2560 g by vertex vaginal delivery after induction of labour because of maternal hypertension and proteinuria. He became tachypnoeic and hypothermic at 12 hours, with a plasma glucose concentration of 1 mmol/l, which failed to rise above 2 mmol/l over the next 48 hours, despite administration of 55 µmol/kg/min of intravenous dextrose. After this his plasma glucose concentration fell to 1·1 mmol/l and he was given a bolus of 0·3 µg/kg of glucagon intravenously after which the plasma glucose concentration rose to 6 mmol/l within 30 minutes and remained above 2·5 mmol/l for the next nine hours. A second bolus of glucagon was necessary when the plasma glucose concentration fell once again, and a glucose turnover study was carried out during this period.

**Case 4.** A girl born by vertex vaginal delivery at 42 weeks' gestation with a birth weight of 3220 g presented with convulsions secondary to hypoglycaemia at 46 hours. Her plasma glucose concentration rose to 2 mmol/l after administration of 33·8 µmol/kg/min of intravenous dextrose but was noted to be extremely labile. In addition, she required repeated 2 ml boluses of 20% intravenous dextrose in an attempt to correct the hypoglycaemia. Phenytoin was administered when further convulsions occurred during these episodes of hypoglycaemia (see later). The first sustained rise of plasma glucose concentration to 3 mmol/l was observed after treatment with a 200 µg/kg bolus of intravenous glucagon. One further episode of hypoglycaemia occurred 48 hours later and the baby was established on full oral feeds by day 10. Plasma glucagon and insulin concentrations were measured during the study.

**Cases 5 and 6.** Case 5 was the sister of case 3 and was born one year later. In view of the history of her brother, her blood glucose concentration was measured after birth and found to be 0 mmol/l. She was treated with glucagon and made an uneventful recovery.

Case 6 had a clinical history that was similar to cases 1–4. Plasma insulin and glucagon concentrations were measured during treatment with glucagon

## Methods

All blood samples were collected from heparinised intravenous cannulae and placed on ice in prechilled fluoride tubes for the glucose and insulin assays. Tubes containing edetic acid and 1000 KIU of aprotinin were used for the glucagon assays The plasma was separated by centrifugation at 4°C and frozen within 20 minutes of collection. The samples were thawed only once and kept on ice during the assays. The total volume of plasma required for the insulin, glucagon, and tracer/total glucose assays was 250 μl.

Total glucose concentrations in the plasma, tracer infusate, and dextrose solutions were measured using a commercially available glucose oxidase spectrophotometric assay (Boehringer-Mannheim) and an Analox LM3 analyser (Analox Instruments). The calibration curve for the glucose oxidase assay was constructed using gravimetric standards (0·5–0·9 mmol/l). A regression analysis showed that differences of 0·4 mmol/l could be measured with a standard error of 0·1 mmol/l. The accuracy of the Analox Analyser was improved by modifying the output to display the glucose concentration to the second decimal place and recalibrating the machine every 10 samples. As an additional check recalibration was carried out if calibration standards (which were inserted every fifth sample) differed by more than 2% from the expected value. All samples were measured at least in duplicate and the standards used were of appropriate composition for the sample being assayed—that is, plasma based standards for plasma samples.

The turnover of glucose was measured using 6,6-dideuteroglucose, which is a non-recycling glucose molecule that is labelled with a stable isotope of hydrogen. It was administered intravenously with a prime dose (30 mg/kg) followed by a continuous infusion at a rate that was small compared with the dextrose administration rate (0·94 μmol/kg/min and 55–83 μmol/kg/min, respectively).

A two hour distribution period was allowed after the priming dose to ensure a steady rate of tracer enrichment within the total glucose pool before any samples were taken. The enrichment of tracer in the plasma samples and the labelled infusates were measured using a Finnigan MAT 4000 combined gas chromatograph and mass spectrometer. The α-D-glucofuranose cyclic 1,2:3,5 bis(butylboronate)-6-acetate derivative was prepared for gas chromatography and the $[M-57]^+$ ions (m/Z 297 and 299 for the unlabelled and labelled derivatives, respectively) were analysed in selected ion monitoring mode on the mass spectrometer using electron impact at 70 eV.

Glucagon concentration was measured using a radioimmunoassay (Novo Research Institute) with $^{125}$I labelled pork glucagon and a rabbit anti-pork glucagon serum K5563. This antibody is specific for pancreatic glucagon. The results for the plasma glucagon concentrations that were at the lower end of the range of our assay are expressed as <60 ng/l or <20 ng/l (depending on the volume of plasma available). Only concentrations above these limits could be reliably distinguished from zero.

Insulin concentration was determined by a double antibody radioimmunoassay[3] with a coefficient variation of 6·5%. The assay was modified by doubling the number of points on the standard curve and increasing the incubation time to improve its accuracy at low concentrations of insulin. This assay could reliably distinguish insulin concentrations of >1·2 μU/ml from zero. All samples for insulin and glucagon were assayed at least in duplicate.

**Calculations of glucose turnover rates.**

*Case 1*

The calculations are based on standard tracer kinetics. The rate of glucose entering the total glucose pool has two inputs, the dextrose infusion rate (Ri) and an unknown endogenous hepatic production rate (Rh). The tracer is infused at a known rate (Rt*). In the steady state the pool size is constant and the total glucose appearance rate (Ra) is equal to the sum of Ri and Rh. Ra is also equal to the disappearance rate of glucose (Rd).

$$\begin{aligned} Ri+Rh &= Ra \qquad (1)\\ &= Rd \end{aligned}$$

Ra can be calculated from the steady state tracer equation[4] shown below

$$RA=\left[\frac{\text{Tracer infusate enrichment}}{\text{Plasma enrichment}}-1\right]Rt^*$$

As Ri is known Rh can be calculated from equation 1.

This equation was used in experiments both before and after administration of diazoxide in case 1.

*Cases 2 and 3*

This steady state tracer equation could not be used to calculate Ra in these babies because the plasma glucose concentrations were not constant. Steele's method for measuring glucose turnover in the non-

Table 2 *Results in case 1 of glucose turnover studies before and after treatment with diazoxide*

| | *Mean (SEM) plasma glucose concentration (mmol/l)* | *Mean (SEM) plasma insulin concentration (μU/ml)* | *Infusion rate of intravenous dextrose (μmol/kg/min)* | *Hepatic glucose production (μmol/kg/min)* |
|---|---|---|---|---|
| Experiment 1 (before diazoxide) | 2·63 (0·01) (n=14) | 4·2 (0·2) (n=5) | 59 | 13 |
| Experiment 2 (diazoxide study) | 6·41 (0·02) (n=9) | <1·2 | 7·6 | 29 |

steady state was employed instead[5] This method is a one compartment approximation of the total glucose pool and requires prior knowledge of the 'pool fraction', a multiplier that is applied to the true volume of distribution of glucose and takes a value between 0 and 1. Animal experiments indicate that the optimum value of the pool fraction is 0·65[6] The computations were performed on a DEC20 mainframe computer using an interactive tracer analysis programme specifically designed by one of us for this task.[7] Equation 1 was then used again to calculate Rh.

The observed data were smoothed by least squares using low order spline functions.[7] The degree of smoothing was such that the average departure of the fitted curve from the observed points was less than the estimated accuracy of the observations themselves.

## Results

**Case 1.** (Table 2.) Before treatment with diazoxide the hepatic glucose production rate was 13 μmol/kg/minute; the normal range for fasting term neonates is 27–44 μmol/kg/minute.[8] This had increased to 28 μmol/kg/minute after treatment The mean (SEM) insulin concentrations before and after treatment were 4·2 (0·2) μU/ml (n=5) and less than 1·2 μU/ml, respectively. The highest observed insulin concentration was 11·8 μU/ml, and this sample was taken at a time when the baby was receiving intravenous dextrose and the glucose concentration was 2·4 mmol/l.

### Cases 2 and 3

The plasma insulin concentrations were only 10 μU/ml in both babies when the dextrose infusion rate was transiently decreased in an attempt to reduce the plasma glucose concentration to below 2 mmol/l. Figures 1 and 2 show that the rate of hepatic glucose production was negligible in both these patients before treatment with intravenous glucagon. This is clearly shown by nearly identical results for total glucose appearance rate as measured by tracer (Ri+Rh) and the known dextrose infusion rate (Ri). Ri is indicated by the dotted line in Figures 1(c) and 2(c) and the rise in hepatic glucose production after glucagon is shown by the divergence of total glucose appearance rate (solid line) and the constant dextrose infusion rate.

This improvement in HGPR was sustained for the rest of the natural history in case 2 as is clearly shown by the ranges of blood glucose in the hours before and after administration of glucagon (0·2–4·3 mmol/l and 4·2–9·8 mmol/l, respectively). Case 3

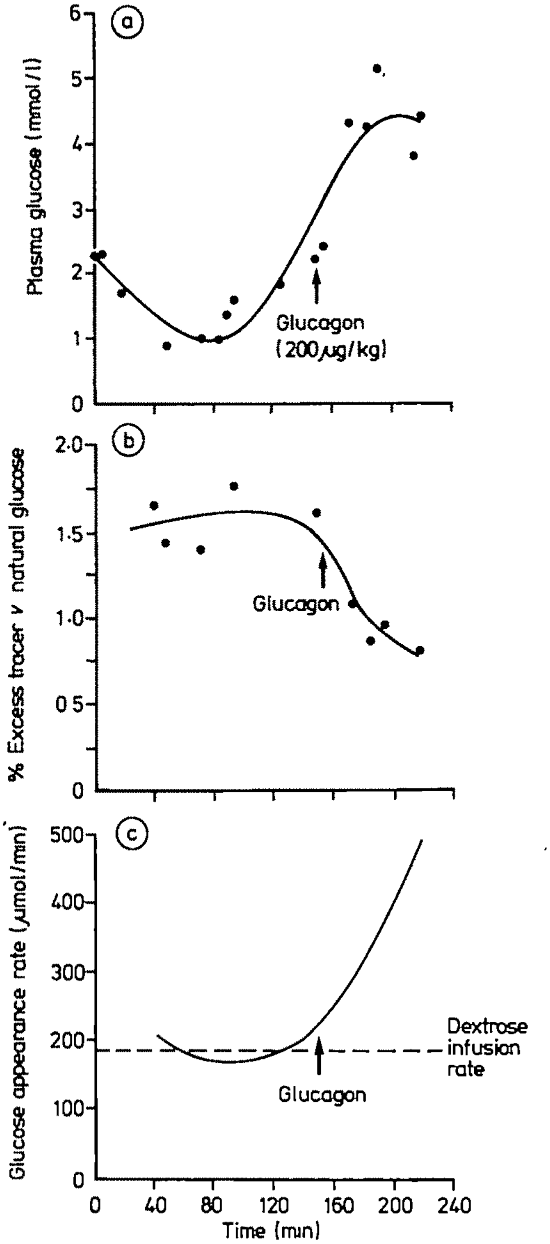

Fig 1 *Results of non-steady state glucose turnover experiments in case 2 (a) Effect of glucagon on plasma glucose; (b) effect of glucagon on tracer enrichment, and (c) change in total glucose appearance rate (Ra—see text) with glucagon The dotted lines in (c) represent the rate of intravenous dextrose administration The difference between the dotted and solid lines is the net hepatic glucose production rate Each arrow marks the time at which glucagon bolus was administered intravenously The plasma insulin concentrations were all <6 μU/ml in the first 100 minutes and <12 μU/ml after treatment*

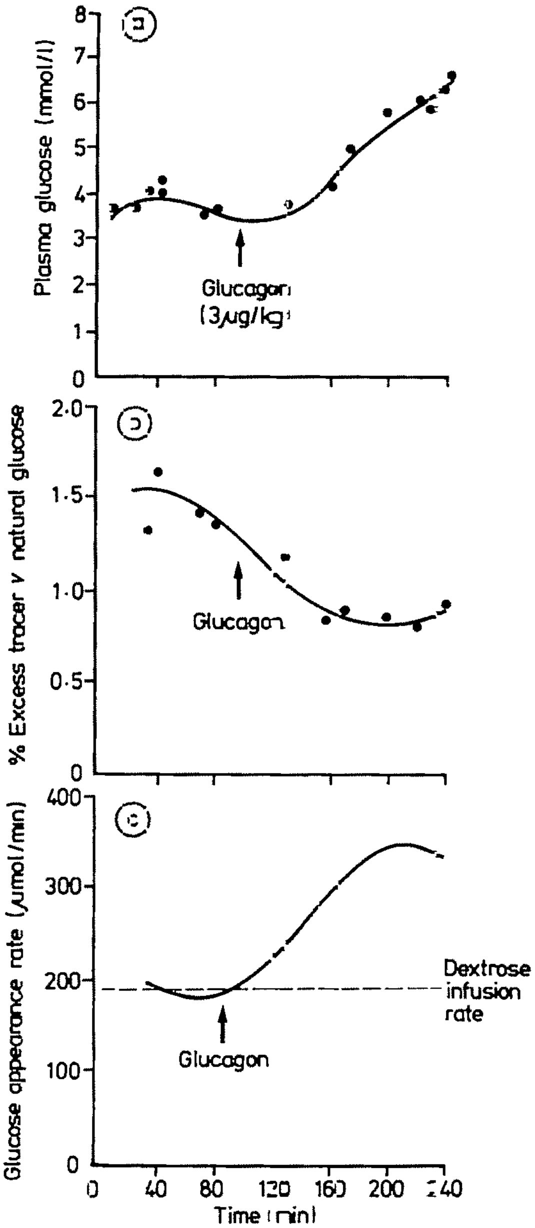

Fig 2 *Results of non-steady state glucose turnover experiments in case 3 (see legend to Fig. 1 for details).*

showed a similar improvement for nine hours after receiving a smaller, more 'physiological' dose of glucagon (1·5% of that given to case 2). The ranges for the pretreatment and post-treatment insulin concentrations were 4–6 and 10–12 μU/ml, respectively, for both babies. These 'normal' concentrations before treatment were observed at a time when the hepatic glucose production rate was zero. The plasma glucagon concentration in case 3 before treatment with glucagon was <60 ng/l.

## Discussion

Previous workers have measured the hepatic glucose production rate in clinically stable neonates who did not have severe hypoglycaemia at term.[8-10] These infants either had normal intravenous dextrose requirements or were able to tolerate short periods of fasting. Kalhan showed a reduction in hepatic glucose production rate in infants of mothers with gestational diabetes,[10] but this complication was not present during pregnancy in any of our babies

The hepatic glucose production rate was low before treatment in all the babies studied here. This was accompanied by a raised glucose disappearance rate (Ri+Rh), and yet in cases 1, 2, and 3 the insulin concentrations were never in the accepted range for hyperinsulinism.[11 12]

The glucagon concentrations were lower than expected for term neonates[13] and may have facilitated excessive insulin activity, despite a low absolute concentration. It is well recognised that it is the molar ratio of glucagon/insulin that is of vital importance in determining the balance of production and consumption of glucose.[14] This argument is also supported by the restoration of hepatic glucose production rate associated with further suppression of a 'normal' insulin concentration using diazoxide in case 1.

The response to a single bolus of glucagon is also interesting because of its sustained effect. Case 2 required only a single bolus (200 μg/kg) and case 3 who had a much lower dose (3 μg/kg), maintained his plasma glucose concentration in the normal range for nine hours. This persistent action may perhaps be explained by the observation that phosphoenolpyruvate carboxykinase (PEPCK) activity, which is essential for gluconeogenesis, is strongly induced by a high glucagon/insulin molar ratio.[15] This ratio is low during fetal life, and postnatal induction of PEPCK occurs in response to the surge of glucagon secretion, which normally occurs after birth.[15]

A previous study showed that the fall in blood glucose concentration shortly after birth was associated with a rise in plasma gluconeogenic amino acids, but no hormone measurements were made at this time.[16] It was suggested that part of the fall in blood glucose was due to a delay in the maturation of gluconeogenic enzymes. These infants were very small for dates, with a mean birth weight of only 2300 g at term, which is much lower than our study group

One of the arguments for not using treatment with glucagon has been that it provokes insulin release, but this is a transient effect[17] and may not be important after treatment in the patient because the molar ratio of the two hormones still favours net glucose release from the liver This is clearly shown in table 3 where the high plasma glucagon concentration of >2000 ng/l was still present three hours after a bolus of glucagon. It is also interesting to note that case 5, the sister of case 3 was born one year later, and also had severe hypoglycaemia at term that responded to treatment with glucagon. The plasma glucagon concentration was <20 ng/l and the insulin concentration was 4 μU/ml at a blood glucose concentration of 0 mmol/l. Both siblings tolerated prolonged fasting a few days after treatment but some familial cause for the lack of glucagon secretion cannot be ruled out in these cases. Vidnes described a case of permanent plasma glucagon deficiency that also had a familial basis,[18] but this child came from a consanguineous marriage, which was not the case in our babies.

Case 4 had already received several boluses of dextrose in the hours before the plasma sample was collected for insulin measurement. The high insulin concentration found in this baby may have been stimulated by the sudden rise in plasma glucose concentration after each bolus. The dextrose infusion rate required to maintain euglycaemia was not excessive (38·8 μmol/kg/min), which is particularly interesting because the baby was on phenytoin at this time to treat the convulsions that had occurred soon after birth. It is not generally realised that this drug suppresses insulin release from the beta cell of the pancreas.[19 20] When the phenytoin was withdrawn the dextrose requirements increased to 83 μmol/kg/min. This has considerable clinical relevance because a high intravenous dextrose requirement is one of the hallmarks of excessive insulin activity The use of phenytoin could easily mask this sign and confuse the clinical picture because hypoglycaemia might then recur as the suppressive effect on the beta cell is lost. This seems to be the most likely explanation for the second episode of hypoglycaemia in case 4 (table 3).

This second episode was associated with a recurrence of the low glucagon concentration (60–80 ng/l) and an inappropriately high insulin concentration (14 μU/ml) for the prevailing blood glucose concentration of 1·6 mmol/l. On day 12 the baby was fasted for four hours and no hypoglycaemia occurred. The plasma glucagon concentration was then in the normal range for term neonates.

We have shown that a reduced hepatic glucose production rate can occur even when the classical diagnostic criteria for the hyperinsulinism are not present. The absolute concentration of insulin during hypoglycaemia is often used as a marker for hyperinsulinism, and it is important to realise that when high insulin concentrations are not present excessive insulin activity can still occur because of glucagon deficiency.

Abnormalities in the mechanisms that control the molar ratio of insulin to glucagon may be of greater importance than 'hyperinsulinism' per se in the pathogenesis of hypoglycaemia in those term neonates who require excessive quantities of intravenous dextrose

The high plasma glucagon concentration after an intravenous bolus initially releases stored glucose (from hepatic glycogen) but may also have a longer term action on the induction of PEPCK, which is a key enzyme in gluconeogenesis.

Intravenous glucagon boluses may be a better initial treatment for unexpected hypoglycaemia in the term neonate because they avoid the rebound hypoglycaemia associated with boluses of dextrose or sudden termination of dextrose infusion.

## Addendum

Since the acceptance of this paper we have studied two infants in greater detail. Both infants had similar histories to our original cases and had

Table 3 *Results in case 4 of plasma glucagon and insulin concentrations during treatment with glucagon*

| | *Insulin (μU/ml)* | *Glucagon (ng/l)* | *Mean (range) glucose (mmol/l)* |
|---|---|---|---|
| *Day 6* | | | |
| Before glucagon | 45 | <60 | 3 28 (3 1–3 46) (n=5) |
| One hour after glucagon | 47 5 | >2000 | 5 23 (3 31–7 56) (n=9) |
| Three hours after glucagon | 4 6 | >2000 | 3 0 (Single sample) |
| *Day 8* | | | |
| During second episode of hypoglycaemia | 14 | 60–80 | 1 6 (Single sample after three hour fast) |
| *Day 12* | | | |
| After recovery | 13 | 190 | 3 86 (Single sample after four hour fast) |

undetectable plasma glucagon concentrations (<20 ng/l) when the HGPR was zero The plasma insulin concentrations were <6 and 14 μU/ml, respectively. A 200 μg/kg bolus of intravenous glucagon produced a sustained rise in HGPR, and plasma glucagon concentrations were within the range 180–240 ng/l at 48 hours when clinical recovery had taken place We see about two cases per year in our hospital, which suggests an incidence of the order of 1 per 1500 live births. We believe that early recognition of transient glucagon deficiency and prompt treatment with intravenous glucagon is of benefit in these infants.

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# Early and late cranial ultrasonographic appearances and outcome in very low birthweight infants

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SUMMARY Of 798 very low birthweight infants admitted to a regional neonatal intensive care unit over a five year period, 547 were discharged home and 524 available for follow up at two to five years later. Eighty-seven infants had a major impairment. Both early and late cerebral ultrasonographic appearances gave useful prognostic information, but the presence of cystic lesions, particularly if bilateral, was highly significant There was a close correlation between late parenchymal lesions and previous ipsilateral intraventricular haemorrhage, suggesting a causal relation.

The introduction of cranial ultrasonography for diagnosing cerebral injuries has resulted in increased awareness of their frequency in very low birthweight infants and of their relevance in predicting neurodevelopmental outcome. Earlier studies emphasised the importance of periventricular haemorrhage.[1–5] Parenchymal cystic lesions seen later in the neonatal period have recently been considered more important than haemorrhage in causing adverse outcome.[6 7] Many of the studies on ultrasonographic appearances and follow up have comprised small numbers of patients or been done over short periods of time, thus not allowing a good estimate of the predictive value of ultrasonographic examination in the neonatal period. Studies have also not taken into account the effect of lesions on one or both sides of the brain, or the association between early haemorrhagic lesions and the later appearance of parenchymal cysts. These factors are important in making an accurate prognosis and attempting to prevent intraventricular haemorrhage.

## Patients and methods

From January 1980 to December 1984, 798 infants weighing less than 1501 g at birth were admitted to this neonatal intensive care unit, and 547 were discharged home No infants were excluded from the study. Seventeen infants subsequently died from various causes including the 'sudden infant death syndrome', infections, non-accidental injury, and accidents Of the remaining 530, 451 (85%) were followed up at the regional unit, 53 (10%) by consultant paediatricians at local hospitals, and the remainder by health visitors assessments, general practitioners' reports, or, in a few cases, questionnaire to the parents. The duration of follow up varied between two and five years.

Follow up at the regional centre comprised neurological and general physical examination, together with developmental screening with the Denver developmental screening test at 1 year and annually thereafter. Specialist referral to the

Table 1 *Classification of early and late ultrasonographic appearances*

| *Grade* | *Description* |
|---|---|
| Early lesions | |
| 0 | Normal |
| Flare | Small, often transient echodensities at upper border of lateral ventricles |
| 1 | Subependymal haemorrhage |
| 2 | Intraventricular haemorrhage |
| 3 | Parenchymal haemorrhage or extension |
| Late lesions | |
| 0 | Normal |
| Persistent ventricular enlargement | Usually irregular or asymetrical, beyond 1 month of age |
| Periventricular leucomalacia | Periventricular cysts, usually multiple and small and not connecting with the ventricle |
| Porencephalic cysts | Large, usually solitary cysts seen often after previous infarction or parenchymal extension of haemorrhage |

regional child development centre was made if neurodevelopmental problems were detected Impairment was defined as a developmental quotient of < 80, cerebral palsy of any degree, or hearing or visual loss likely to impair developmental progress. Severe developmental delay was considered to be equivalent to a developmental quotient of 50 or less, and moderate developmental delay was a developmental quotient of 51–80. Four children had chromosomal disorders or syndromes, and two were severely impaired postnatally by non-accidental injury and excluded from this analysis. The follow up assessments are the result of pooled reports from several sources for some cases.

All infants had a cranial ultrasonographic examination on admission to the unit, daily for the first week of life, and weekly or more often until discharge. Ultrasonography was performed by me or by a lecturer or research fellow supervised by me The time of the babies' discharge varied, but those discharged early often had ultrasonographic examinations at their first or second follow up visit,

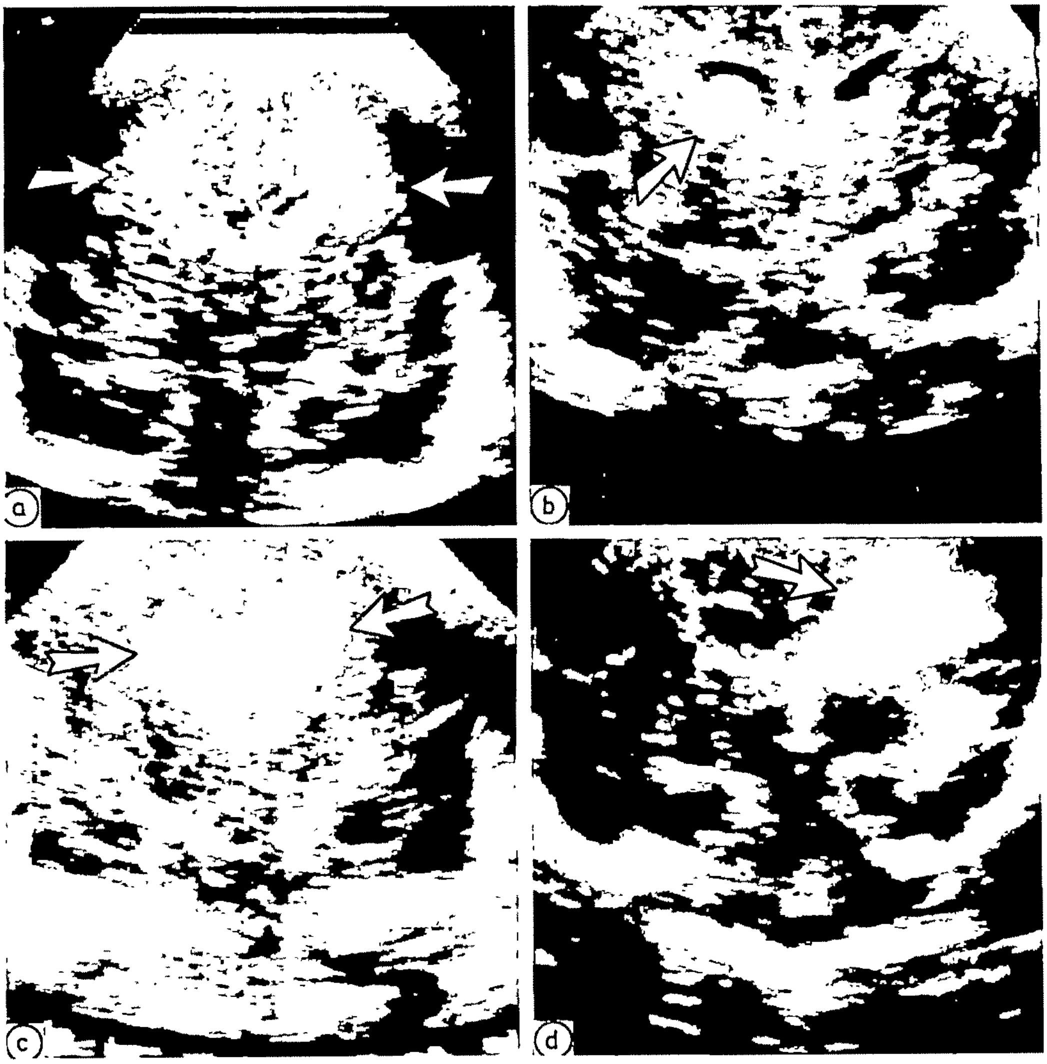
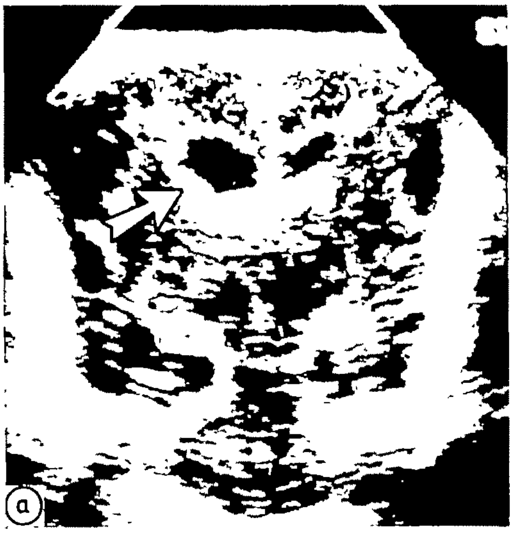


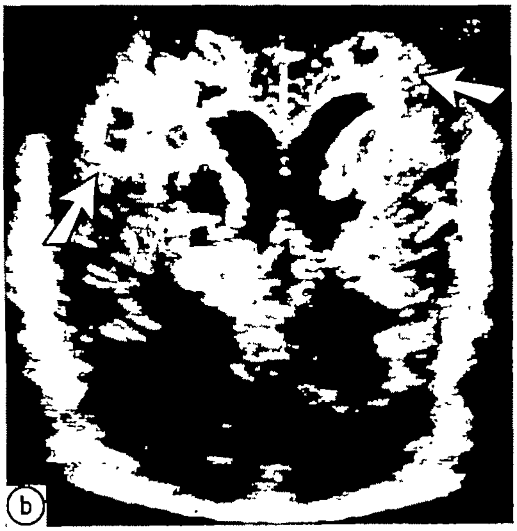
Fig 1a *Early ultrasound appearances bilateral 'flares'.* Fig 1b *Early ultrasound appearances unilateral subependymal haemorrhage (grade 1)* Fig. 1c *Early ultrasound appearances bilateral intraventricular haemorrhage (grade 2)* Fig 1d *Early ultrasound appearances. unilateral parenchymal haemorrhage (grade 3).*

but only if previous abnormalities had been detected. Infants weighing $< 1500$ g at birth were rarely discharged at less than 2 weeks of age, and usually much later. All babies referred from other hospitals were admitted before the third day of life and most of them on the day of birth. An Advanced Technology Laboratories (ATL) 805A mechanical sector scanner with 5 or 7·5 MHz transducers was used. A written record of each examination was kept together with Polaroid photographs of changes as they occurred. Appearances were designated 'early', representing mainly haemorrhagic lesions and occurring during the first week of life, and 'late', representing parenchymal lesions probably due to cerebral ischaemia or atrophy and first visible from the second week onwards Table 1 shows the classification, which is illustrated in figs 1 and 2. Only coronal sections are shown, but sections in the midline, parasaggital, and tangential parasaggital planes were also used to complete the diagnosis. Differences in proportions of impairments with different ultrasonographic appearances were analysed with the $\chi^2$ test unless otherwise stated, and a probability of $< 0{\cdot}05$ was accepted as significant.

## Results

Five hundred and twenty-four infants were available





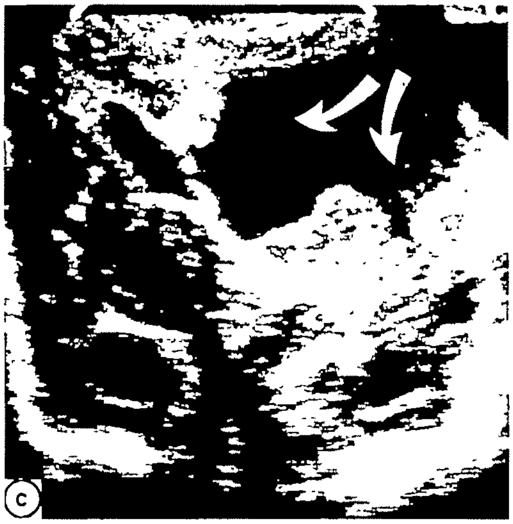


Fig 2a *Late ultrasound appearances. persistent ventricular enlargement*

Fig 2b *Late ultrasound appearances periventricular leucomalacia.*

Fig 2c *Late ultrasound appearances. porencephalic cyst*

for follow up, and information from at least one source was available on all of them. Of these, 87 infants had an impairment 50 had cerebral palsy, 39 had moderate developmental delay, 17 had severe developmental delay, 12 were blind (six from retinopathy and six with presumed cortical blindness), 11 had bilateral severe deafness, and 12 had epilepsy. Several infants had more than one impairment.

When early ultrasonographic appearances were correlated with later impairment a significant trend to greater prevalence of impairment was seen with increasing grades of haemorrhage, ($p < 0{\cdot}001$, table 2). Table 2 also shows the 95% confidence intervals for the prevalence of impairment in each ultrasound group. Bilateral grade 2 or 3 haemorrhage in the first week of life is more likely to result in impairment (table 1). Different grades of haemorrhage were almost exactly symmetrically distributed between right and left sides of the brain. Minor as well as major grades of haemorrhage were associated with some increase in the risk of later impairment, but this was usually because parenchymal lesions developed later. There was a significant correlation between the grade of early haemorrhage not affecting the parenchyma and the later occurrence of parenchymal lesions on the same side of the brain ($p < 0{\cdot}001$, table 3) No such correlation was seen with parenchymal lesions on the opposite side of the brain. This suggests a causal association between early haemorrhage and the later development of ipsilateral parenchymal lesions

When late ultrasonographic appearances were correlated with subsequent impairments a similar significant trend to greater prevalence with increasing size of the lesion was seen ($p < 0{\cdot}001$, table 4).

Periventricular leucomalacia was first seen at a median of 15 days (range 4–50 days n = 47). Bilateral cystic lesions (periventricular leucomalacia or porencephalic cysts) greatly increase the risk of impairment. Most infants with impairments at follow up had either cerebral palsy or moderate or severe developmental delay.

Developmental delay was significantly associated with cystic lesions ($p < 0{\cdot}001$) particularly when they occurred bilaterally rather than unilaterally (Fisher's exact test, $p < 0{\cdot}004$) (table 4). Similar associations were seen with cerebral palsy. Porencephalic cysts were more likely to result in cerebral palsy than periventricular leucomalacia. The incidence of cerebral palsy after bilateral lesions of any sort was higher than that after unilateral lesions Evidence of early haemorrhage, and late ultrasonographic appearances, had similar sensitivi-

Table 3 *Association between early periventricular haemorrhage and late parenchymal lesions on ipsilateral side of brain*

| | *0* | *Late parenchymal lesions* | |
|---|---|---|---|
| | | *PVE*<br>*No (%)* | *Cystic (PVL and PC)*<br>*No (%)* |
| Grade of haemorrhage | | | |
| 0 | 372 | 8 (2%) | 10 (2·5%) |
| 1 | 48 | 5 (8·5%) | 6 (10%) |
| 2 | 43 | 14 (21%) | 18 (27%) |

PVE = Persistent ventricular enlargement
PVL = Periventricular leucomalacia
PC = Porencephalic cyst

Table 2 *Early ultrasound appearances and major impairments*

| *Diagnosis* | *Grade of haemorrhage*<br>*0*<br>*(n = 333)* | *Flare*<br>*(n = 13)* | *1*<br>*(n = 73)* | *2*<br>*(n = 73)* | *3*<br>*(n = 32)* | *Unilateral*<br>*2 or 3*<br>*(n = 56)* | *Bilateral*<br>*3/2 or 3/3*<br>*(n = 11)* |
|---|---|---|---|---|---|---|---|
| Normal | 314 | 12 | 59 | 43 | 9 | 32 | 2 |
| Moderate DD | 11 | 0 | 6 | 11 | 11 | 10 | 4 |
| (DQ < 80) | (3 3, 1 8–6 5) | | (8 2, 3 2–17 7) | (15, 7 5–24 7) | (34, 18 6–53 2) | (18, 9–30 9) | (36, 10 9–69 3) |
| Severe DD | 2 | 0 | 8 | 4 | 6 | 2 | |
| (DQ < 50) | (0 6, 0 08–2 4) | | (4 1 0 9–12) | (10 9, 5–21 3) | (12 5, 3 5–29) | (10·7, 4 1–22 2) | (18 1, 2 3–51·8) |
| Cerebral palsy | 10 | 1 | 6 | 13 | 20 | 15 | 9 |
| | (3 6, 1 6–6 0) | | (8 2, 3 2–17 7) | (17 8, 9 6–28 3) | (62 5, 43 7–78 8) | (26 8, 15 9–40 6) | (81 8, 48 2–97 7) |
| Deaf | 0 | 0 | 2 | 5 | 4 | 4 | 1 |
| Blind | 1 | 0 | 1 | 8 | 2 | 4 | 1 |
| Any major impairment | 19 | 1 | 14 | 30 | 23 | 24 | 9 |
| | (5 7, 3 6–9 3) | (7 7: 0 2–36) | (19 2 10 9–29 7) | (41 1, 29 7–52 9) | (71 9, 57 5–83 7) | (42 8, 29 7–57 0) | (81 8, 48 2–97 8) |

Figures in parentheses are percentage incidence and 95% confidence intervals for each group
DD = development delay
DQ = developmental quotient.

Table 4 *Later ultrasound appearances and major impairments*

| | *Ultrasound appearances* | | | | | |
|---|---|---|---|---|---|---|
| *Diagnosis* | *0 (n = 418)* | *Persistent ventricular enlargement (n = 40)* | *Periventricular leucomalacia (n = 34)* | *Porencephalic cyst (n = 32)* | *Cystic lesions (PVL and PC)* | |
| | | | | | *Unilateral (n = 42)* | *Bilateral (n = 24)* |
| Normal | 382 | 32 | 16 | 7 | 20 | 3 |
| Moderate DD | 16 | 4 | 10 | 9 | 12 | 7 |
| (DQ < 80) | (3·8, 2·2–6·8) | (10, 2·8–23·7) | (29·4, 19·1–41·6) | (28·1, 13·7–46·7) | (28·6, 15·7–44·6) | (29·2, 12·6–51) |
| Severe DD | 5 | 0 | 4 | 8 | 1 | 11 |
| (DQ < 50) | (1·2, 0·3–2·5) | | (11·8, 3·2–26·7) | (25, 11·5–43·4) | (2·4, 0·06–13·1) | (45·8, 25·6–67·2) |
| Cerebral | 17 | 5 | 6 | 22 | 13 | 15 |
| palsy | (4, 2·2–6·8) | (12·5, 4·2–26·8) | (17·6, 6·5–33·6) | (68·7, 50–83·8) | (30·9, 17·6–47) | (62, 40·6–81·2) |
| Deaf | 4 | 1 | 3 | 3 | 6 | 0 |
| Blind | 3 | 0 | 5 | 4 | 1 | 8 |
| Any major | 36 | 8 | 18 | 25 | 22 | 21 |
| impairments | (8·6, 6·4–12·2) | (20, 9–36) | (52·9, 35–70) | (78·1, 60–91) | (52·4, 1–66·6) | (87·5, 66·6–97·3) |

Figures in parentheses are percentage incidence and 95% confidence intervals for each group
DD = development delay, PVL = periventricular leucomalacia, PL = porencephalic cyst, DQ = developmental quotient

Table 5 *Sensitivity and specificity of early and late ultrasound appearances in predicting later impairments*

| | *All impairments* | | *Severe developmental delay* | | *Cerebral palsy* | |
|---|---|---|---|---|---|---|
| | *Sensitivity (%)* | *Specificity (%)* | *Sensitivity (%)* | *Specificity (%)* | *Sensitivity (%)* | *Specificity (%)* |
| Grade 2 or 3 PVH | 61 | 92 | 71 | 82 | 66 | 96 |
| Late cystic lesion (PVL or PC) | 49 | 90 | 70 | 99 | 56 | 95 |

PVH = periventricular haemorrhage, PVL = periventricular leucomalacia, PC = porencephalic cyst

Table 6 *Types of cerebral palsy and ultrasound lesions observed*

| | *No ultrasound lesions* | *PVH only* | *Late ultrasound lesions* |
|---|---|---|---|
| Diplegia (n = 15) | 6 | 4 | 5 |
| Hemiplegia (n = 26) | 2 | 3 | 21 |
| Quadriplegia and others (n = 9) | 1 | 1 | 7 |

PVH = periventricular haemorrhage

ties and specificities in predicting impairments (table 5). Spastic diplegia (n = 15) was more often seen in infants without late ultrasonographic abnormalities, whereas hemiplegia (n = 26) and quadriplegia (n = 9) were usually associated with late parenchymal lesions This difference was significant (Fisher's exact test $p < 0.0045$, table 6).

## Discussion

When portable ultrasonography machines became available to neonatologists less than 10 years ago they replaced computed axial tomography as the main method of diagnosing cerebral haemorrhagic and ischaemic lesions because less invasive and more frequent examinations could be made. The first reports concentrated on the incidence of periventricular haemorrhage and factors associated with its occurrence.[1 8–10] Subsequent studies concentrated on the association between the early findings of haemorrhage and outcome.[2–5 11–12] In some of these studies 'outcome' concerned early death rather than developmental progress in later years, and in others the small number of subjects studied did not allow confident prediction of outcome. In similar groups of very low birthweight infants conclusions such as that all parenchymal haemorrhages are fatal,[5] smaller haemorrhages are not associated with poorer outcome,[11] smaller haemorrhages are associated with poorer outcome,[5] and ventricular dilatation[13] or parenchymal cystic lesions[6 7] are the main determinants of outcome may all be found.

To assemble sufficient numbers of infants for examination of outcome by subgroups an investigation such as this must continue over several years in a large centre This produces several methodological problems. Ultrasonographic equipment is constantly improving. For the first three and a half years of the period covered by this study a 5 MHz transducer was used; subsequently a 7·5 MHz transducer was used with theoretically, better linear resolution. The proportion of infants with areas of cystic degeneration diagnosed remained substantially the same in each year of the study, although more 'flares' were noted later in the study The interpretation of results also changed over the five year period, periventricular leucomalacia being recorded as 'cerebral atrophy' or 'irregular ventricles' in the early part of the study and a four point scale of severity for periventricular haemorrhage being used With the publication of pathological correlation studies the nomenclature used in this paper was adopted, and previous ultrasonographic pictures were reclassified using the Polaroid records and the contemporary written reports.

Infants with impairments seen at follow up comprised 10% of the original group admitted to the unit, and most had ultrasonographic abnormalities in the perinatal period Whether early or late ultrasonographic appearances are used as predictors of later impairment, the sensitivity and specificity are similar (table 5) This is important as if this information is to be taken into account when making clinical decisions about management it is required early rather than late in the neonatal period. The occurrence of later impairments in infants with early lesions not affecting the parenchyma seems to be associated almost entirely with the subsequent development of periventricular leucomalacia. That a significant relation exists between the extent of early and late appearances in the same infant, but only when the same side of the brain is considered, is strongly suggestive that this association is causal (table 3). The release of vasoactive substances by thrombi produced from early periventricular haemorrhage may produce local ischaemia and late periventricular leucomalacia. Preventing periventricular haemorrhage, or blocking the release or effects of substances released from thrombi, may limit the development of subsequent lesions and their neurodevelopmental sequelae. Severe local cerebral ischaemia at the site of previous cerebral haemorrhage has been shown by positron emission tomography.[14]

Because of the number of infants included in this study it was possible to consider the predictive value of ultrasonographic appearances for specific neurodevelopmental problems rather than for major problems generally. The presence of late cystic lesions was strongly predictive of developmental delay, and this association was more obvious when the lesions were bilateral. Bilateral lesions were more than twice as likely to be followed by developmental delay as unilateral ones, but, more importantly, in most of these cases the impairment was severe (table 4). The severe effect of bilateral lesions on intellectual prognosis may simply be related to the extent of the original brain injury, or be because both sides of the neonatal brain possess cognitive functions which may in part be preserved in unilateral lesions.

The prevalence of cerebral palsy should correlate well with cerebral ultrasonographic findings, particularly late cystic changes. Of the 50 infants with cerebral palsy at follow up, 33% had late lesions, which suggested that they had been caused by perinatal events In nine infants, however, no ultrasonographic abnormalities were seen. This could be because the abnormalities were beyond the resolution of the machine used, or because they occurred after the infants had been discharged from the unit. Alternatively, cerebral palsy may in some cases be caused by aetiological events outside the perinatal period. Support for the latter view comes from the distribution of late ultrasonographic lesions between types of cerebral palsy Cystic appearances were strongly associated with spastic hemiplegia and quadriplegia but significantly less so with spastic diplegia, suggesting different aetiologies. The median length of stay of the 15 infants with spastic diplegia was 40 days (range 11–120 days), making early discharge an unlikely reason for missing later ultrasonographic changes In addition, the infants with diplegia who had cystic lesions also had developmental delay. Only one of the 10 diplegic infants, whose pictures did not show cysts had developmental delay at follow up.

Visual defects occurred in 12 infants. When these were due to severe retinopathy of prematurity some periventricular bleeding was always seen, but none of the infants had extensive late cystic lesions. In all six infants with presumed cortical blindness extensive cystic lesions were present. Retinopathy may be associated with free blood in the central nervous system, which produces local vasospasm and retinal injury in much the same way as early ventricular haemorrhage may lead to later ischaemic lesions. Cortical blindness is caused by extensive disruption of tracts and has been described in association with bilateral subcortical cystic lesions.[6 7]

Bilateral severe deafness was present in 11 infants and was usually associated with extensive periventricular haemorrhage, though not necessarily later cystic lesions. Such an association has been described previously and was attributed to blood entering the inner ear [15] Convulsions without fever occurred in 12 infants, all of whom had cystic parenchymal lesions or post haemorrhagic hydrocephalus.

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# Acarboxyprothrombin activity after oral prophylactic vitamin K

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SUMMARY The effect of prophylaxis with oral vitamin K (1 mg vitamin $K_1$ given with the first feed) on the rate of detection of acarboxyprothrombin (PIVKA II) and factor II clotting activity were analysed. Introducing such prophylaxis reduced the rates of detection of PIVKA II activity on day 5 from 48% to zero. None of the babies given prophylaxis had factor II clotting activity below 40%, compared with 34 of 95 babies not given prophylaxis. This study has important implications in the prophylaxis of both classical and late onset haemorrhagic disease of the newborn.

The need for prophylaxis with vitamin K has recently been reaffirmed.[1] There is, however, controversy as to how the vitamin should be given Several authors have argued that oral instead of parenteral administration would spare babies the discomfort and potential risk of intramuscular or subcutaneous injections.[2 3] Fairly good absorption of vitamin K given orally to healthy neonates has recently been reported.[2] Variation between subjects, however, was considerable, and the safety of oral vitamin K prophylaxis has therefore been questioned [4]

In this study we assessed the effect of prophylaxis with oral vitamin K on the vitamin K supply of the neonate by analysing acarboxyprothrombin (PIVKA II) activity, a marker for vitamin K deficiency; we also used a coagulation test for factor II.

## Patients and methods

PIVKA II and clotting analyses were performed in healthy 5 day old full term infants. We first looked at the detection rates of PIVKA II and factor II clotting activity in 95 neonates not given vitamin K prophylaxis from May to September 1985. We then compared the effect of oral prophylaxis (1 mg vitamin $K_1$ with first feed) on these measurements in a further 95 babies from May to September 1986. The influence of potential seasonal changes could be excluded as both groups were studied during the same months of the year. The Table shows that there were no significant differences in mean birth weights or methods of feeding (breast, formula, or mixed) between the two groups. Blood samples for measurement of PIVKA II activity and factor II clotting analysis were taken from a heel prick on day 5, at the same time as the compulsory blood sampling for screening tests for inherited disorders of metabolism and hypothyroidism.

PIVKA II activity was determined with crossed immunoelectrophoresis as described previously.[5] A whole blood clotting assay was used for factor II analysis.[6]

All mothers had given informed consent both to the blood sampling and to the vitamin K regimen.

Table 1 *Comparison of two groups of healthy full term infants*

| *Group* | *Mean (SD) birth weight (g)* | *No breast fed* | *No breast and formula fed* | *No formula fed only* |
|---|---|---|---|---|
| A (no prophylaxis) | 3[illegible]70 (399) | [illegible] | 23 | 8 |
| B (1 mg vitamin $K_1$ orally with first feed) | 3[illegible]80 (403) | [illegible] | 21 | 9 |

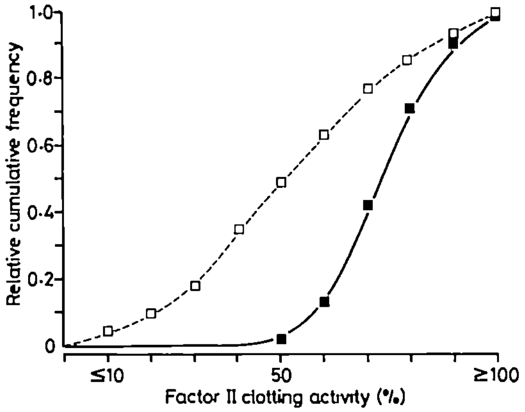

Figure *Association between factor II clotting activities in 5 day old healthy neonates and oral prophylaxis with vitamin $K_1$. □ no vitamin K prophylaxis, ■ 1 mg vitamin $K_1$ with first feed*

The study was approved by the local ethical committee.

## Results

Of 95 healthy babies not given vitamin K prophylaxis, 47 showed PIVKA II activity, none of the 95 babies given oral vitamin K did.

The cumulative distribution patterns of factor II clotting activity in babies who had and had not been given prophylactic vitamin K are shown in the Figure. None of the babies given vitamin K had factor II clotting activity below 40%, compared with 34 of the 95 babies not given vitamin K. Five of these babies, all exclusively breast fed, had severe hypoprothrombinaemia with factor II clotting activity of less than 10%.

## Discussion

High detection rates of PIVKA II activity in healthy 5 and 6 day old neonates not given vitamin K prophylaxis at birth have been reported.[7] Apart from confirming these results, our data additionally give clear evidence of severe hypoprothrombinaemia in several of the babies with PIVKA II activity. This prompted us to introduce vitamin K prophylaxis and to evaluate the effect of an oral regimen.

Oral and intramuscular vitamin K prophylaxis have been shown to have similar effects on clotting factors dependent on vitamin K.[8] Using a more sensitive marker for vitamin K deficiency (PIVKA II activity), however, Motohara *et al* reported a detection rate of PIVKA II activity of 11·4% in babies given 5 mg vitamin $K_2$ orally at birth.[9] This prompted us to evaluate the effect of prophylaxis with oral vitamin K by giving a 1 mg dose of vitamin $K_1$, the only vitamin K preparation available in Europe. In our study all 95 babies given 1 mg vitamin $K_1$ with the first feed had no PIVKA II activity detectable on the fifth day of life and had normal factor II clotting activity. Though the blood sample may have been taken after the nadir of clotting factors dependent on vitamin K, vitamin K deficiency on previous days would not have escaped detection as PIVKA II has a 50% disappearance rate of about 50 hours.[10] These data therefore suggest that oral vitamin $K_1$ given as a 1 mg dose with the first feed protects against vitamin K deficiency in the neonatal period.

Several explanations might account for the high detection rates of PIVKA II activity in the series reported by Motohara *et al.*[9] Firstly, the method might not be specific enough to differentiate between neonatal prothrombin and PIVKA II activity. Secondly, some of the PIVKA II results on day 5 might arise from intrauterine vitamin K deficiency, as PIVKA II activity was found in 19·2% of the corresponding samples of cord blood with the enzyme linked immunosorbent assay used by Motohara *et al.*[9] With our method PIVKA II activity was not detectable in cord blood and interference with PIVKA II activity indicating anamnestic vitamin K deficiency therefore was unlikely.[7] Finally, the absorption and metabolism of vitamin $K_2$ might be different from that of vitamin $K_1$.

Even for vitamin $K_1$, however, the absorption in healthy babies varied widely,[3] but this does not seem to matter for the supply of vitamin K in the neonatal period. It might, however, be relevant to late onset vitamin K deficiency, a bleeding disorder that often presents with intracranial haemorrhage in 4–8 week old infants. Three observations (below) related to five cases of bleeding due to late onset vitamin K deficiency in this hospital cast doubt on the ability of prophylaxis with oral vitamin K to prevent late onset vitamin K deficiency.

Massive bleeding after a sample of venous blood had been taken was diagnosed in a 25 day old boy who had received 2 mg vitamin K orally with the first feed. Partial thromboplastin time and prothrombin time were prolonged, and vitamin K deficiency was proved when these measurements returned to normal within four hours of subcutaneous injection of 1 mg vitamin $K_1$. This boy had been fed on a formula not supplemented with vitamin K. He showed no clinical symptoms of malabsorption and had not received any antibiotics. At the time the late onset vitamin K deficiency was diagnosed he had mild cholestasis with slightly abnormal liver function test results, which could not be attributed to bile duct atresia, viral hepatitis, cystic fibrosis, or α-1-antitrypsin deficiency.

Intracranial haemorrhage due to late onset vitamin K deficiency was diagnosed in a 45 day old boy who had been given 3 mg vitamin $K_1$ orally 24 days before the life threatening bleeding occurred [11] The boy, who had not been given vitamin K prophylaxis at birth, first presented with bleeding from an insect bite when 21 days old. Coagulation studies initially showed prolonged prothrombin and partial thromboplastin times, but these returned to normal after treatment with oral vitamin K and were still normal one week later. On the forty fifth day, however, he had an intracranial haemorrhage due to vitamin K deficiency. The boy, who had been exclusively breast fed, had mild symptoms of liver disease and abnormal liver function test results due to α-1-antitrypsin deficiency. Although oral vitamin K had not been given at birth, it seems unlikely that a smaller prophylactic dose given three weeks earlier would have been effective in preventing the intracranial haemorrhage.

Massive umbilical bleeding due to vitamin K deficiency was diagnosed in a 13 day old, breast fed girl. Hypoprothrombinaemia responded promptly to oral treatment with 2 mg vitamin $K_1$. Vitamin K deficiency, however, recurred four times despite treatment with oral vitamin K after each episode. Although no prophylactic oral vitamin K had been given before the initial bleeding, it seems unlikely that prophylaxis at birth would have been effective in preventing the bleeding as recurrent vitamin K deficiency after oral vitamin K prophylaxis could be due to malabsorption of the vitamin.[12]

Parenteral vitamin K was safe and provided the babies with a high dose of vitamin K[3]; this might account for the fact that late onset vitamin K deficiency is rarely observed in babies given intramuscular prophylaxis, and it is certainly wiser to continue parenteral prophylaxis until the equivalent dose of oral vitamin K has been established to prevent late onset vitamin K deficiency.

The data presented in this paper encourage further studies to evaluate an appropriate dose regimen for oral vitamin K prophylaxis Pharmacological studies[3] and clinical experience, however, suggest that much higher or repeated oral doses are required to protect against late onset vitamin K deficiency.

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# Recent trends in the incidence of multiple births and associated mortality

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SUMMARY The overall incidence of multiple births in England and Wales, which had been declining since the early 1950s, started to increase in the early 1980s in all age groups except for women under 20. This followed a rise in the incidence of triplet and higher order multiple births which had started in the late 1970s. Analyses of data for births between 1978 and 1983 showed that while stillbirth, perinatal, neonatal, and post-neonatal mortalities among multiple births fell considerably, they remained consistently higher than those for singleton births. Differences in the distribution of birth weight do not wholly explain these differences. Analyses of certified causes of stillbirth and death are difficult to interpret because a considerable proportion were attributed to 'multiple pregnancy'.

In England and Wales the collection of data about multiple births began in July 1938 when the Population (Statistics) Act came into force This Act was passed at a time of public concern about falling birth rates to collect additional data about parents so that fertility could be monitored more closely. The rationale for analysing multiple births was firmly set in this context: 'Although fertility is usually measured by the number of children born rather than by the number of maternities experienced, it is necessary to remember that the former is a composite total made up of the number of maternities, which is susceptible to voluntary control and the number of extra children born in multiple maternities which cannot be so readily controlled'.[1]

Interest soon moved to multiple births themselves and many analyses of these trends have been published.[1–11] Nevertheless, although death rates among multiple birth babies under the age of 1 year were analysed as part of a special study of births in 1949 and 1950,[12] these rates were not analysed routinely until 1975.[7]

In this paper we consider trends and changes in the incidence of multiple births in England and Wales and analyse subsequent mortality among them from 1975–83.

## Registration of infant births and deaths

When births are registered in England and Wales the number of babies delivered and whether each was live or stillborn are recorded. The Office of Population Censuses and Surveys (OPCS) also collects data about twins and triplets for computer analysis, by allocating a code to categorise the genders of the babies in each set, and whether they were live or stillborn. The exception is data about births in 1981, which were not coded because of industrial action by local registrars of births and deaths. Since 1975 the OPCS has routinely linked records of infant deaths (deaths of babies under the age of 1 year) registered in each calendar year to the data collected when the births were registered.[13] These 'linked records', together with stillbirth records, are amalgamated into a data file that is used to correlate the deaths with information collected when the birth was registered such as the age of the parents, place of delivery, and whether the baby was part of a multiple birth.

This linked file is referred to as the 'death cohort'. From this file a second linked file is produced; this is referred to as the 'birth cohort' and contains all records of deaths of babies born in a given year. This is more useful for the analysis of multiple births as babies within a given set may die in different calendar years even though the deaths occurred before the babies reached the age of 1 year.

Multiple births may not be fully represented in registration data because under the Births and

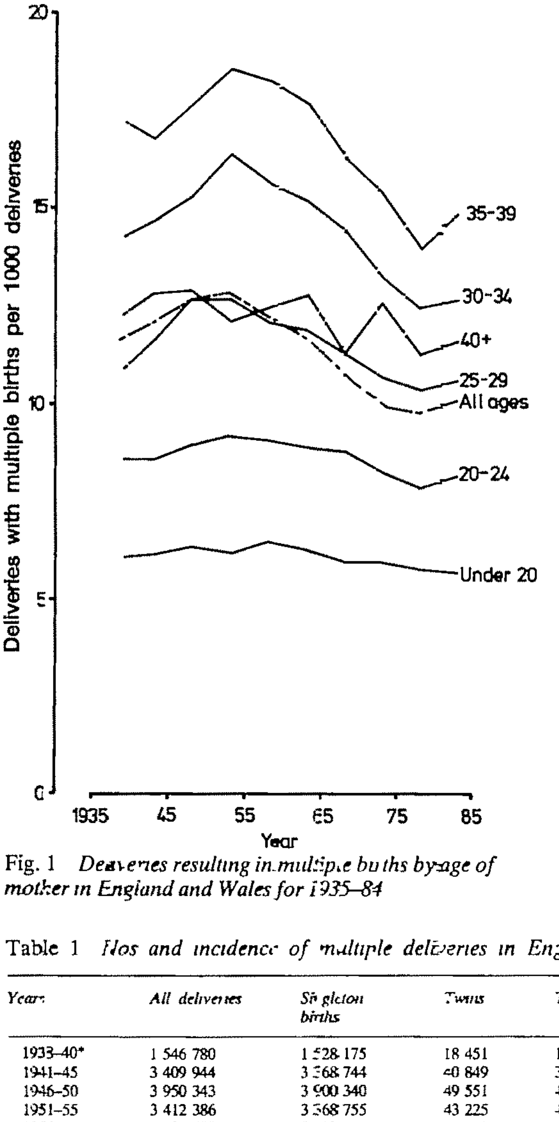


Fig. 1 *Deliveries resulting in multiple births by age of mother in England and Wales for 1935–84*

Deaths Registration Acts in force in England and Wales fetal deaths are not registrable as stillbirths if they occur before 28 completed weeks of gestation, although live births are. Thus if a multiple birth, including both live and dead fetuses, occurs before 28 weeks of gestation only the live births are registered. Despite this an analysis of the 803 sets of twins born in 1975–78 where one twin was stillborn showed an unexpectedly high number of sets where the gestational age of the stillbirth was given as 28 weeks (gestational age is not collected for live births) This suggests that some of the twins may have been born after a shorter gestation, but the age was stated to be 28 weeks on the stillbirth certificate so that both babies could be registered.

## Trends in the incidence of multiple births

The proportion of deliveries with multiple births rose from 1938 until the early 1950s, and then fell until the late 1970s. Figure 1 shows that this occurred in births to women in all age groups, although in those aged 40 or over a less regular pattern was seen. The proportion of deliveries resulting in multiple births in 1982–84 was higher than in 1976–80 among deliveries in all age groups except those aged under 20.

Table 1 shows that trends in the proportion of pregnancies resulting in twins showed a similar pattern, the proportion resulting in triplets had already started to rise in the late 1970s. Numbers of sets of quadruplets had also risen much more

Table 1 *Nos and incidence of multiple deliveries in England and Wales during 1938–85*

| *Years* | *All deliveries* | *Singleton births* | *Twins* | *Triplets* | *Quadruplets* | *Quintuplets* | *Sextuplets* |
|---|---|---|---|---|---|---|---|
| 1938–40* | 1 546 780 | 1 528 175 | 18 451 | 153 | 1 | | |
| 1941–45 | 3 409 944 | 3 368 744 | 40 849 | 343 | 8 | | |
| 1946–50 | 3 950 343 | 3 900 340 | 49 551 | 444 | 8 | | |
| 1951–55 | 3 412 386 | 3 368 755 | 43 225 | 401 | 4 | 1 | |
| 1956–60 | 3 732 859 | 3 687 188 | 45 240 | 427 | 4 | | |
| 1961–65 | 4 267 306 | 4 217 736 | 49 116 | 443 | 6 | | |
| 1966–70 | 4 097 511 | 4 053 556 | 43 533 | 413 | 6 | 1 | 2 |
| 1971–75 | 3 433 182 | 3 398 786 | 34 020 | 353 | 19 | 4 | |
| 1976–80 | 3 040 236 | 3 010 581 | 29 253 | 373 | 24 | 4 | 1 |
| 1982–85 | 2 536 895 | 2 511 092 | 25 515 | 332 | 22 | 2 | 2 |
| Rates per 1000 deliveries | | | | | | | |
| 1938–40 | | 988 0 | 11 9 | 0 10 | | | |
| 1941–45 | | 987 9 | 12 0 | 0 10 | | | |
| 1946–50 | | 987 3 | 12 5 | 0 11 | | | |
| 1951–55 | | 987 2 | 12 7 | 0 12 | | | |
| 1956–60 | | 987 8 | 12 1 | 0 11 | | | |
| 1961–65 | | 988 4 | 11 5 | 0 11 | | | |
| 1966–70 | | 989 3 | 10 6 | 0 10 | | | |
| 1971–75 | | 990 0 | 9 9 | 0 11 | | | |
| 1976–80 | | 990 2 | 9 6 | 0 13 | | | |
| 1982–85 | | 989 8 | 10 1 | 0 14 | | | |

*From July 1938 onwards, triplets and above
Source OPCS Birth Statistics Series FM1

noticeably; while only six sets were born in 1961–65 and a further six in 1966–70, 19 were born in 1971–75 and 24 in 1976–80.

Although the zygosity of multiple births is not recorded at birth registration, in many analyses the numbers of monozygous (identical) twins have been estimated using Weinberg's method, which subtracts the number of different sex pairs from the number of pairs of the same sex.[14] This assumes that the number of different sex, dizygous (non-identical) twins born in a given time period equals the number of same sex dizygous pairs born in the same period. Analyses based on these assumptions suggested that birth rates of dizygotic twins started to fall in England and Wales in the late 1950s and early 1960s, while those of monozygotic twins remained constant. This was still true after allowing for the mothers' ages and parities, and similar trends were observed in several other countries.[9–11]

The halt in the decline in the overall incidence of twin births in England and Wales in the mid-1970s was commented on in 1983 in a letter to the *Lancet*, which reported similar trends in Scotland and Canada.[15] The reply pointed out that if the analysis was confined to twins of different sex and allowance was made for mother's age, then there was no sign of a halt in the decline.[16]

Figure 2 shows more recent trends in estimated incidence of monozygotic and dizygotic twin births, which suggest that overall, the rate of dizygotic twin births may have levelled off, while the monozygotic rate increased in the late 1970s and early 1980s. Analysis within maternal age groups, however, shows a less clear picture.

## Mortality in multiple births

Multiple births tend to be preterm and of low birth weight, which means that multiple birth babies are at increased risk of being stillborn or of dying in the first year of life than singletons.

Figure 3 shows perinatal and infant mortality for births between 1975 and 1983. The ratio of multiple birth perinatal death rates to those for singleton births remained fairly constant over the period, with the rate for multiple births being about five times that of singleton births. The highest excess mortality for multiple births occurred in the neonatal period,

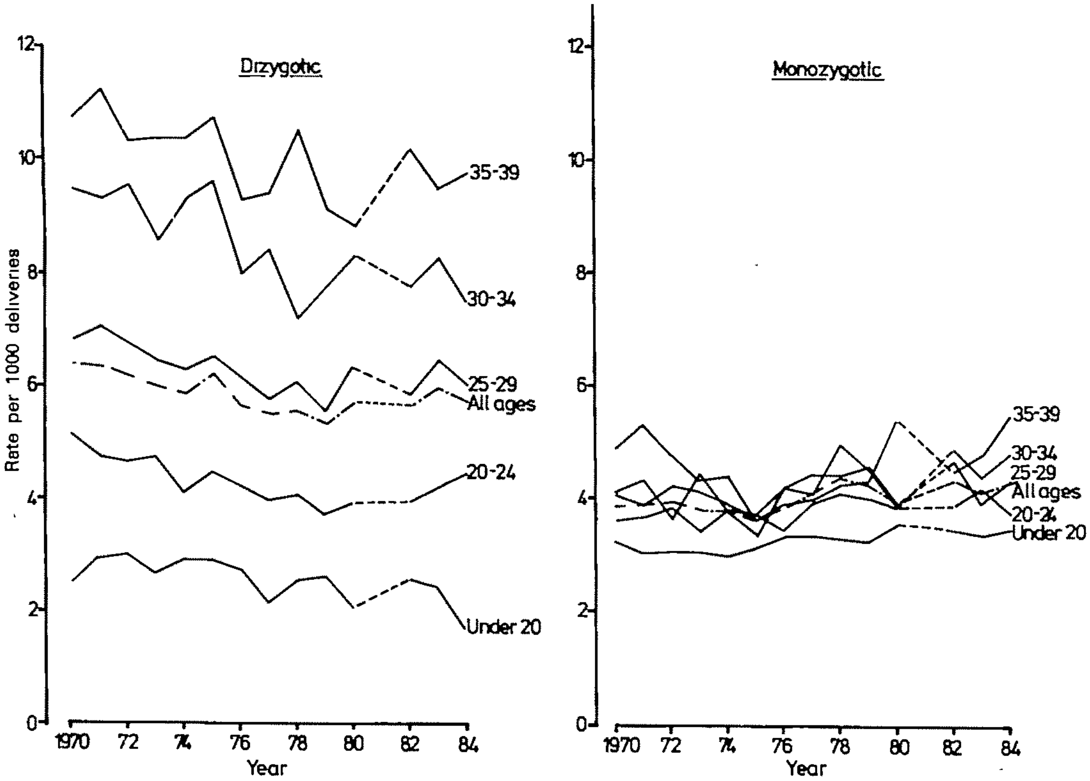
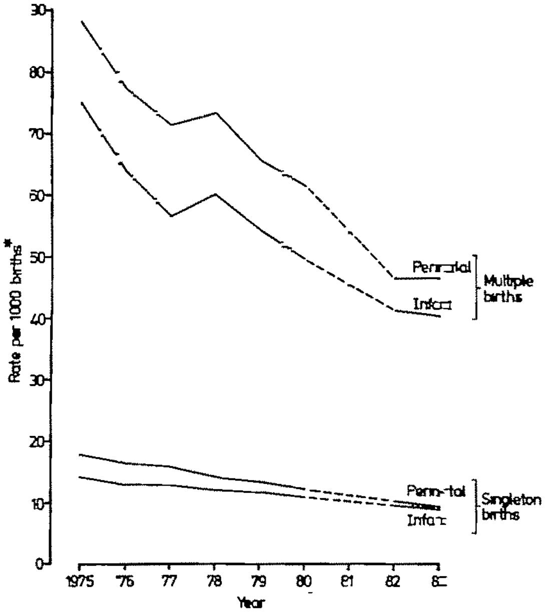


Fig 2 *Birth rates of estimated dizygotic and monozygotic twins by age of mother in England and Wales for 1970–84*

despite the neonatal death rates for multiple births reducing from seven times that of singleton births to under six times between 1975 and 1983. This reduction resulted in the ratio of infant mortality for multiple:singleton births declining from 5·3:1 to 4·3:1. Postneonatal mortality for multiple births expressed as a percentage of singleton births actually increased slightly.



*Perinatal rate per 1000 live and stillbirths
Infant rate per 1000 live births

Fig 3 *Perinatal and infant mortality among singleton and multiple births in England and Wales for 1975–83.*

Perhaps the increased mortality of multiple births in the neonatal period can be accounted for by differences in birth weight.[17] Information on birth weight in England and Wales has been collected by OPCS only since 1975. Initially, many data were missing but the position has steadily improved. By 1983 over 99% of live births, 98% of stillbirths, and 96% of infant deaths had the birth weight recorded.

Just over half the multiple birth babies born between 1982 and 1984 weighed less than 2500 g, compared with 6% of singleton births. Table 2 shows births and perinatal deaths in these years tabulated by birth weight. Within each 500 g grouping under 2500 g babies born in a multiple birth had significantly lower perinatal mortality than singletons ($p<0{\cdot}0001$), using the standard normal deviate. For babies weighing 2500–3499 g, the difference between the two rates for singletons and multiple births was no greater than would be expected by chance ($p<0{\cdot}05$). In the two groups with the heaviest birth weight mortality was much higher for multiple births than for singleton births, but the rates for multiple births were based on only small numbers of deaths.

In general, mortality declined sharply as birth weight increased, the high proportion of low birthweight babies in multiple births leading to higher overall perinatal mortality than for singletons. Nevertheless, standardising to singleton birth weight specific rates, shows that only 74% of the expected perinatal deaths actually occurred. This was due to the reduced mortality of multiple birth babies weighing under 2500 g compared with that of singletons. Thus in England and Wales the increased perinatal mortality associated with multiple births was not simply a consequence of their birth weight.

Table 2 *Perinatal deaths by birth weight for single and multiple births in England and Wales for 1982–84 combined*

| *Type* | *Birth weight (g)* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *All* | *Under 1500* | *1500–1999* | *2000–2499* | *2500–2999* | *3000–3499* | *3500–3999* | *4000 and over* | *Not stated* |
| *Perinatal deaths:* | | | | | | | | | |
| Singleton | 18 323 | 6102 | 2367 | 2448 | 2492 | 2115 | 1072 | 469 | 1258 |
| Multiple | 1738 | 1051 | 243 | 151 | 93 | 22 | 15 | 3 | 158 |
| *Total births* | | | | | | | | | |
| Singleton | 1 864 683 | 15 697 | 20 152 | 75 979 | 335 553 | 716 064 | 511 141 | 160 874 | 28 803 |
| Multiple | 38 413 | 3206 | 5114 | 11 187 | 12 499 | 4848 | 725 | 45 | 787 |
| *Rates/1000 total births:* | | | | | | | | | |
| Singleton | 9 8 | 383 7 | 117 5 | 32 2 | 7 4 | 3 0 | 2 1 | 2 9 | 43 7 |
| Multiple | 45 2 | 327 8 | 47 5 | 13 5 | 7 4 | 4 5 | 20 7 | 66 7 | 200 8 |
| *Expected No of perinatal deaths to multiple births** | | | | | | | | | |
| | 2350 0 | 1245 2 | 600 5 | 360 2 | 92 5 | 14 5 | 1 5 | 0 1 | 34 4 |
| *Ratio of observed to expected × 100* | | | | | | | | | |
| | 74 0 | 84 3 | 40 3 | 41 9 | 100 5 | 151 7 | 1000 0 | 3000 0 | 459 3 |

*Using singleton rates as standard
Source OPCS Monitors, Series DH3

Table 3 shows the overall mortality for 1975 to 1983 for multiple births according to type. As expected, the rates for triplets and higher order births were higher than those for twins Those for quadruplets and higher order births are based on very small numbers of births (41 sets of quadruplets, four sets of quintuplets, and two sets of sextuplets) and thus should be assessed with extreme caution.

## Twins

In 1983 twins accounted for 1% of deliveries and 2% of births, but 9% of perinatal deaths. This represents a perinatal mortality of 46·8 per 1000 multiple births compared with one of 9·6 per 1000 singleton births. During 1975–83 there were notable decreases in stillbirth, perinatal, neonatal, and infant mortality in twins, with falls of 32, 47, 51, and 44% respectively, but little change in their postneonatal mortality.

The 1958 British Perinatal Mortality Survey showed that preterm delivery was a major factor associated with deaths in twins[18] Table 4 shows the underlying causes of death between 1979 and 1984, according to the ninth revision of the *International Classification of Diseases* (ICD).[19] Unfortunately, many of the deaths were attributed to 'multiple pregnancy'. This accounted for 27% of stillbirths, 25% of perinatal deaths, and 21% of neonatal deaths. The most commonly attributed causes of stillbirth were complications of placenta and cord. A cause of perinatal death often mentioned was respiratory distress syndrome; this was also the most commonly given cause of neonatal death. This pattern was also reflected in deaths of twins between 1975 and 1978 when the underlying cause was selected using the eighth revision of the *International Classification of Diseases.*

Inspection of individual death certificates for all twins born in 1978 showed that the allocation of underlying cause of death in the neonatal period between multiple pregnancy and respiratory distress syndrome was somewhat arbitrary. It seemed to depend on whether multiple pregnancy was mentioned among the causes of death and, if it was not, whether the various deaths in a multiple birth were recognised as such. This was more likely to have happened if the deaths had been registered on the same occasion. If twins died in the post-neonatal

Table 3 *Mortality for singleton and multiple births in England and Wales for 1975–83 (excluding 1981)*

| *Type of birth* | *Stillbirth** | *Perinatal** | *Neonatal†* | *Postneonatal†* | *Infant†* | *No of births (live and still)* |
|---|---|---|---|---|---|---|
| Singleton | 7 7 | 13 8 | 7 4 | 4 3 | 11 7 | 4 845 382 |
| Twin | 25 4 | 63 2 | 43 9 | 9 1 | 52 9 | 95 312 |
| Triplet | 47 5 | 164 5 | 135 0 | 12 7 | 147 7 | 1812 |
| Quadruplet | 30 5 | 219 5 | 207 5 | 12 6 | 220 1 | 164 |
| Quintuplet | — | 200 0 | 200 0 | — | 200 0 | 20 |
| Sextuplet | — | 416 7 | 500 0 | — | 500 0 | 12 |

*Rates per 1000 total births, †rates per 1000 live births
Source OPCS series FM1 and DH3 Annual Reference Volumes

Table 4 *Mortality among twins by age and cause in England and Wales for 1979–84 (excluding 1981)*

| *Diseases* | *Cause of death* | *Age at death* | | | | |
|---|---|---|---|---|---|---|
| | | *Stillbirth* | *Perinatal* | *Neonatal* | *Postneonatal* | *Infant* |
| 001–999 | All causes | 1359 | 3151 | 2127 | 538 | 2665 |
| 460–519 | Respiratory conditions | — | 8 | 24 | 123 | 147 |
| 740–759 | Congenital anomalies | 139 | 301 | 219 | 76 | 295 |
| 760–779 | Perinatal conditions | 1220 | 2816 | 1829 | 56 | 1885 |
| 760 | Maternal conditions | 114 | 124 | 10 | — | 10 |
| 761 | Maternal complications in pregnancy | 397 | 846 | 453 | 9 | 462 |
| 761 5 | Multiple pregnancy | 361 | 801 | 444 | 9 | 453 |
| 762 | Complications of placenta and cord | 467 | 508 | 42 | — | 42 |
| 764–5 | Slow fetal growth, fetal malnutrition, and immaturity | 25 | 126 | 113 | 2 | 115 |
| 768 | Intrauterine hypoxia and birth asphyxia | 121 | 224 | 118 | 4 | 122 |
| 769 | Respiratory distress syndrome | — | 469 | 573 | 11 | 584 |
| 770 | Other respiratory conditions | 3 | 179 | 200 | 12 | 212 |
| REM760–779 | Other perinatal conditions | 93 | 313 | 320 | 18 | 338 |
| 798 | Sudden death, cause unknown | — | — | 7 | 193 | 200 |

Source Unpublished OPCS data

period the commonly cited causes of death were the same as for singletons: respiratory conditions, sudden infant deaths, and congenital anomalies.

OPCS does not collect information on zygosity, but it is possible to compare the mortality of pairs of twins of the same and different sexes Apart from postneonatal mortality in girls, the mortality based on deaths in 1982–84 of twins of the same sex was higher than for twins of the corresponding sex born in pairs of mixed gender.

## Triplets

Between 1975–83 (excluding 1981) 5% of babies in registered triplet sets were stillborn. Over the same period 15% of liveborn triplets died in the first year of life, 83% of those dying in the first week of life. This represents a risk of stillbirth double that of twins and six times that of singletons Brown and Daw[20] reported that in 1971–75 in England and Wales the stillbirth rate for triplets was four times that of singleton births. Between 1975–83, the increased risk of infant mortality for babies born in a triplet delivery was three times that of twins and 19 times that of singletons During the period of highest risk, the first week of life, a liveborn triplet was 20 times more likely to die than a singleton, and three times more likely to die than a twin. Although postneonatal mortality is higher among triplets than among singletons, the numbers are small, with only 22 postneonatal deaths of triplets in the eight years under consideration.

Triplet mortality fluctuated throughout the period 1975–83, probably because of various factors, including the sex and zygosity of sets, gestational age, birth weight, and availability of facilities for the care of very small babies. As an average of only 75 sets of triplets were born each year these factors are likely to have fluctuated annually.

As with twins, zygosity of triplets is not recorded at birth registration, but the sex combination of the sets is known. Those triplet sets which contain both males and females must have at least one dizygous pairing Triplets can be monozygotic, dizygotic, or trizygotic, and sets containing both sexes must be either dizygotic or trizygotic.

Table 5 shows that mortality was higher in sets of the same sex (three boys or three girls) than in sets of mixed gender Although 287 of the 604 sets of triplets were identical sex sets, 52 of the 86 stillbirths were in identical sex sets. The Table also shows that among boys mortality was generally higher, but postneonatal mortality was based on a total of only nine male and 13 females deaths. Of the 1812 triplets born in England and Wales in 1975–83, 911 were girls; hence the number of male and female infants was about the same, and female triplets seemed to have a better chance of survival.

When mortality among triplets from 1979–84 was analysed according to underlying cause of death a pattern similar to that for twins was found; 43% of stillbirths, 40% of perinatal deaths, and 34% of neonatal deaths were attributed to 'multiple pregnancy'. Other commonly attributed causes of stillbirth were complications of placenta and cord, and respiratory distress syndrome was often given as a cause of neonatal death The death certificates of triplets born in 1978 again showed a degree of arbitrariness in the allocation of the underlying cause of death between multiple pregnancy and respiratory distress syndrome.

Between 1975–83 an average of 69% of triplet sets survived the first year of life There was, however, a fall in the proportion of triplet sets with one or more stillbirth or infant deaths; 76% of triplets born in 1983 survived after the first year of life, compared with 62% of triplets born in 1975. This was due largely to a reduction in the number of sets in which all the babies died; the number of sets in which one or two died remained fairly constant.

The higher perinatal mortality among triplets may be due to immaturity, but this does not explain the differences in mortality when analysed by birth order. Table 6 shows mortality among triplets by birth order and sex combination within the set. Although this information is not available from the

Table 5 *Mortality among triplets by age, sex, and sex combination of set in England and Wales for 1975–83 (excluding 1981)*

| *Sex Combination* | *Stillbirth* | | *Perinatal* | | *Neonatal* | | *Postneonatal* | | *Infant* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Male* | *Female* | *Male* | *Female* | *Male* | *Female* | *Male* | *Female* | *Male* | *Female* |
| All | 46 5 | 48 4 | 175 2 | [illegible]4 9 | 147 7 | 123 0 | 10 5 | 15 0 | 158 1 | 138 6 |
| 3 male | 54 0 | — | 203 1 | — | 162 7 | — | 14 2 | — | 176 9 | — |
| 2 male–1 female | 22 9 | 7 6 | 145 0 | 105 9 | 136 7 | 107 [illegible] | 3 9 | 23 1 | 140 1 | 130 8 |
| 1 male–2 female | 37 4 | 53 5 | 149 7 | 141 7 | 127 7 | 110 [illegible] | 11 1 | 16·9 | 138 8 | 127 1 |
| 3 female | — | 56 8 | — | 182 7 | — | 141 [illegible] | — | 10 5 | — | 151 8 |

Source Unpublished OPCS data

Table 6 *Mortality among triplets by birth order and sex combination of set in England and Wales for 1975–83 (excluding 1981)*

| *Sex combination* | *Sets registered* | *Stillbirths or infant deaths (No where all babies in set died)* | *Birth order* | | | |
|---|---|---|---|---|---|---|
| | | | *First* | *Second* | *Third* | *Not known* |
| All | 604 | 341 (174) | 84 | 99 | 108 | 50 |
| 3 male | 152 | 103 (57) | 26 | 30 | 30 | 17 |
| 2 male+1 female | 128 | 60 (36) | 16 | 18 | 21 | 5 |
| 1 male+2 female | 189 | 97 (36) | 22 | 26 | 30 | 19 |
| 3 female | 135 | 81 (45) | 20 | 25 | 27 | 9 |

Source Unpublished OPCS data

files held on computer, it was possible to do the analysis manually because of the small numbers Unfortunately, the birth order may not be clear for sets in which there were stillbirths: for some sets, with both live and stillbirths, the birth order of the stillbirth can be deduced from the certificate. For each sex combination, the first born had a better chance of survival than the second child, who in turn had a better (in one case equal) chance of survival than the third.

## Quadruplet and higher order births

There were 41 sets of quadruplets registered, among which there were five stillbirths and 35 infant deaths, giving perinatal and infant mortality of about 1/5. In 27 sets (66%) all the babies survived, and in seven sets (17%) all the babies died

Four sets of quintuplets and two sets of sextuplets had also been registered. In one quintuplet set comprising four boys and a girl and one set of three boys and two girls, all the babies survived the first year. The two other sets of quintuplets comprised two boys and three girls; in one set one girl died during the first week, in the other only the two heaviest babies (one boy and one girl) survived. Of the two sets of sextuplets, one set (three boys and three girls born prematurely) all died within one week of birth. The other set (six girls) survived the first year.

## Discussion

**Trends in the incidence of multiple births.** Figs. 1 and 2 suggest that parity may explain the trends shown. The OPCS records data about parity only for legitimate births, however, and restricts its definition to births by the mother's present or any previous husband The considerable increase in the number of births outside marriage renders such data unreliable. It is, however, worth considering other explanations advanced for the trends observed.

An editorial in the *British Medical Journal* in 1976 on the 'worldwide decline in dizygotic twinning', commented that, 'it is disquieting that something should have affected the human reproductive system for 15 years without anyone having any evidence of what it is' [21] Several explanations were suggested, one of which was the use of oral contraceptives, but this was dismissed on the grounds that in many countries the decline had preceded the introduction of oral contraceptives.

A recent study of 4428 women delivering at five large hospitals in Connecticut, United States of America, found an increased rate of twins among women conceiving within two months of stopping oral contraception.[22] A postal survey in the United States of America confirmed this finding.[23] Other research, however, suggests the opposite. A case control study in France compared women having singleton and twin births and found significant negative associations between the incidence of dizygous twins and the previous use of oral contraceptives.[24] [25] Similar results from other studies were cited. In contrast, a study in Nottinghamshire failed to show any association, either positive or negative, between the incidence of twins and recent use of oral contraceptives.[26]

A second explanation for the decline in the incidence of dizygotic twins came in a series of papers by W H James, who suggested that an environmental agent might have played a part—perhaps a pesticide, or stilboestrol used in cattle feed.[9–11] He also dismissed the suggestion that the decline in the incidence of dizygotic twins might be a consequence of increased rates of spontaneous abortions. It is difficult to compare time trends in the absence of any consistent or complete series of routinely collected data about trends in spontaneous abortion.[7] A cross sectional study comparing the rates of twin births and spontaneous abortion in 22 towns of the South Moraven region of Czechoslovakia showed that those with higher numbers of spontaneous abortions had lower numbers of twin births,[27] although there may have been variations in the notifications of spontaneous abortion.[5]

Different explanations have been advanced for the recent increase in triplet and higher order births and these may also apply to the upturn in the rate of twin births. Induction of ovulation using fertility drugs increases the risks of multiple births.[26 28 29] There is a need for better monitoring of infertility treatment[31] and techniques are being developed for the selective termination of some of the fetuses in a multiple pregnancy.[31] In addition, in vitro fertilisation techniques entailing the implantation of more than one embryo can lead to multiple pregnancy, but, such pregnancies may not yet be common enough to increase perceptibly the proportion of multiple births. The association between the incidence of multiple births and mothers' ages and parities and the problems in assessing the effect of parity has been alluded to.[32] Racial differences can also play a part; studies in the United States and Africa have shown that multiple births are more common among black, than among white and Asian women.[33–37] Rates are particularly high in some parts of Africa. Such comparisons are not possible in England and Wales where parents' countries of birth are recorded but not their ethnic origin. Thus the probably growing numbers of births to black women of Afro-Caribbean descent who were themselves born in the United Kingdom cannot be analysed.

A study of multiple births in Scotland during 1962–64 suggested that the number of births of dizygotic twins was associated with social class, being highest among women with husbands in partly skilled or unskilled manual occupations.[38] It was suggested that different social class patterns of fertility may have been responsible. The OPCS is currently analysing more recent trends in social class differences in twins of the same and different sexes.

**Mortality in multiple births.** Mortality patterns similar to those shown in table 2 can be seen in the mortality of single and twin births in the 1958 British Perinatal Mortality Survey,[18] and in a study of births from 1950–60 in New York state.[39] In both cases the problems of comparing mortality by birth weight from two populations with different birth weight distributions have to be borne in mind.[40] In addition, in table 2, mortality for multiple birth babies weighing 3500 g or more was based on only 18 deaths in a three year period, and these may well have been babies with exceptional problems.

In the 1958 survey mortality was also analysed by gestational age, and it was shown to be higher for single births at 28 to 32 weeks' gestation and for twins at 39 weeks and above. It is not possible to repeat this analysis using more recent data, as gestational age is not recorded at the registration of live births in England and Wales. Data from the 1958 survey showed that the relation between birth weight and gestational age was different for singleton and multiple births.

**Twins.** The higher mortality among twins born in pairs of the same sex compared with those born in mixed sets may be due to differences in zygosity. Monochorionic monozygous twins are in close proximity in the uterus and may suffer because of their communicating placental circulation; dichorionic monozygous pairs and dizygous pairs may have adjacent implantation sites. Babies born in mixed set pairs will necessarily be dizygous, while those born in single sexed sets will be a mixture of dizygous and monozygous.

Another analysis of mortality among twins in the 1958 British Perinatal Mortality Survey compared the mortality of first and second twins.[18] It showed that at all weights, except 2001–2500 g, the mortality was higher among second twins. It has not been possible to do a similar analysis using more recent data as the OPCS records the time of birth only for live multiple births.

As the OPCS does not collect data on gestation for live births we cannot examine certified causes of death at different gestation times. Nevertheless, the results shown in table 4 are compatible with Laursen's findings that neonatal deaths among twins born before 36 weeks' gestation were nearly all attributable to respiratory failure, whereas for those born at or after 36 weeks' gestation, most stillbirths were attributable to intrauterine placental insufficiency.[41]

**Triplets.** The higher mortality of second and third triplets may be due to their less favourable position in the uterus during labour, rendering them more liable to direct trauma from the contracting uterus during delivery.[42] Another factor is the reduction of uterine capacity following delivery of the first triplet, which might alter the blood flow in the placenta and thus cause anoxia in the remaining babies. This could be aggravated by the cumulative effect of prolonged anaesthesia.

As with twins, the higher mortality among sets of the same sex suggests that mortality among triplets is highest in monozygous sets. The higher mortality among boys was also reported by Daw.[43] His finding that girls predominated in triplet births, however, may well have arisen from the fact that his analysis was based on a relatively small number of sets of triplets.

**Conclusions.** There is no firm evidence for or against any of the hypotheses about the decrease in the incidence of multiple births between the early 1950s and the late 1970s, or the more recent increase. The correlation between the introduction of drugs to treat infertility and the rise in triplet and higher order births is compatible with the suggestion that these drugs, and more recently in vitro fertilisation, may have played a part. Furthermore, the absence of any increases in the overall incidence of multiple births in women under the age of 20 lends further support to this. Unfortunately, it is difficult to pursue this further because of the dearth of national information about the extent and outcome of treatment for infertility.[7, 30, 44]

In an attempt to compensate for this deficiency we plan to collect some information about the extent of investigations and treatment for infertility among parents of triplet and higher order births and matched samples of singleton and twin births for the years 1979–80 and 1982–85. This is being done as part of a wider study of the medical and social problems associated with triplet and higher order births.

To make better assessments of trends in mortality several improvements could be made within the existing system. Firstly, a more complete picture would be obtained if mortality could be calculated according to birth order within a multiple birth. The OPCS could only do this if the manual recording of time of birth at registration of multiple live births was extended to stillbirths, and if these data were included on the computer record for live and stillbirths.

Secondly, the accuracy of the information about cause of death recorded on certificates could be improved. New forms of certificate were introduced in January 1986 for certifying stillbirths and neonatal deaths in England and Wales, which will provide scope for providing fuller and more detailed information. In particular, we hope that the custom of attributing stillbirths and deaths to 'multiple pregnancy' will be replaced by more precise indications of the conditions leading to death.

Finally, fuller analyses would be possible if, as the World Health Organisation recommends,[19] gestational age of livebirths were recorded at registration. Alternatively, this information could be obtained in the future if the data currently collected at birth registration were to be linked to the maternity data collected through the new system being set up, following the recommendations of the Steering Group on Health Services Information.[45]

While these fuller data would be useful to indicate the way forward; the data presented in this paper show an encouraging picture of declining perinatal and infant mortality among babies born in multiple births. There are, however, no routinely collected data about disability or childhood illness among children born in a multiple birth. These will be investigated in the Study of Triplet and Higher Order Births.

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# Sudden infant death syndrome in south east Scotland

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SUMMARY Three hundred and fifty eight infants from south east Scotland who died suddenly were classified into four groups. Categories for these groups ranged from where a definite cause of death had been recorded to where no explanation had been provided and no associated disorder was discovered (SIDS). Our results supported the view that there are few differences in the history of cases certified as SIDS and other cases reported as dying suddenly but with an explanation. Groups that most closely matched the SIDS definition employed were reported to be healthier throughout life and freer from illness in the 48 hours before death. From the findings of this study the 'true' SIDS group did not appear as an 'at risk' population. The study group as a whole was not marked by social deprivation, poor mothering, or less privileged families. The importance of intensive investigation, including postmortem examination was emphasised, as misdiagnosis may give a 'falsely' inflated picture of the incidence of the syndrome and could cause unnecessary anxiety.

A definition commonly employed in the identification of instances of the sudden infant death syndrome (SIDS) is that proposed in Seattle in 1969:

> "The sudden death of any infant or young child which is unexpected by history, and in which a thorough post-mortem examination fails to reveal an adequate cause of death."[1]

In this study data from a group of infants who died suddenly and unexpectedly and who presented as cases of SIDS were analysed to determine to what extent they matched the above definition and to study any differences detected.

The criterion for the diagnosis of SIDS was necessarily pathological as each infant's death was unexpected by history. To carry out this investigation and enable discrimination between the pathological findings, four categories of classification were employed. These classifications, A, AB, B, and C, enabled analysis of the various findings and study of the extent to which each may have contributed to the death.

The variables used as parameters for comparison between the groups were selected on the basis of their citation in reviews that dealt with SIDS where possible risk factors, such as preterm delivery, mother's age less than 20 years, and poor social conditions surrounding the family, have been indicated.[2 3]

## Procedure

From 1977 to 1985, 358 infants aged between 1 week and 2 years who died suddenly and unexpectedly in south east Scotland were referred by the procurator fiscal for postmortem examination. These infants, all of whom presented as cases of SIDS, represented 80% of fiscal referrals. The 20%, that were excluded failed to meet fully the definition of SIDS given above.

Each case underwent radiological, bacteriological, and virological studies. Biochemical estimates of the sodium, potassium, and urea concentrations in the vitreous humour of the eye were obtained and a detailed postmortem examination performed by a paediatric pathologist. Data on each case were abstracted from obstetric and paediatric records about the pregnancy and birth and any further admissions for the infant An extensive protocol was used that covered the mothers' antenatal history, parity, interval to last live birth, and regularity of clinic attendances. Problems during pregnancy, such as hypertension, urinary infection, anaemia, and admissions to hospital, were noted.

For the infant, data about mode of birth, gestational age, birth weight, and admissions to the special care baby unit were recorded. Subsequent admissions to hospital were noted by cause, duration of stay, and interval from discharge to death

Each family doctor was sent a proforma for completion, which dealt with the mother's previous medical and social history and provided for details regarding any problems with the infant and the family. The health visitors also received a form on which to record their knowledge of the family and infant history, including attendance at the health clinic and visits to the home.

A letter was written to each family with the offer of a visit to the home. This visit was undertaken in every case by the same experienced interviewer two to three weeks after the death when a full history was taken about the infant's health, feeding patterns, circumstances surrounding the death, and household and social organisation of the family. An estimate was made of the reliability and facility of the parents' recall. In 27 cases (7%) a visit was not carried out as the families had either left the area or intimated their wish not to be interviewed.

Classification into one of four groups was carried out after the interviews and investigations had been completed to reduce the possibility of bias on the part of the investigators.

Group A (26 cases) comprised those cases where a definite cause of death was ascertained. Group AB (53 cases) comprised those cases where an associated disorder was detected that may have been a factor in the death. Group B (193 cases) comprised those cases where an associated disorder was present but was not thought to be an adequate cause of death. Group C (86 cases) comprised those cases where no observable associated disorder was present.

Analysis of the data relating to each variable was carried out to determine whether or not significant differences existed between the groups. Statistical procedures were based on Freund and Scheffé.[4 5]

The classification of cases into group A was made where an adequate cause of death was found. These deaths, though presenting as SIDS, could no longer be certified as such as they did not completely match the definition. Causes of death in this group were infections (10 cases), Reye's syndrome (five), congenital cardiac defects (four), myocarditis (two) and one each of Waterhouse-Friderichsen syndrome, malnutrition, hypernatraemic dehydration, laryngeal cysts, and a ribbon impacted in the larynx.

The inclusion of cases into group AB relied on the judgment of the pathologist about the severity of the disease process present and the extent of its contribution to death. This was generally assessed histologically. As stated in one report 'there can be doubt and ambiguity, even after a thorough paediatric post-mortem, as to what constitutes an adequate cause of death'.[6] Most postmortem examinations in this study were undertaken by the same prosector, which gave uniformity to both the performance and interpretation of the examination and contributed to the reliability of the findings. A pathogen was isolated and histological evidence of infection shown in 39 cases (73·6%) in this group. In the other 14 cases (26·4%) a variety of other diagnoses were found, such as a degree of nephrocalcinosis, inhalation of vomit, or metabolic disorders, but in no instance was the condition thought to be severe enough to be an adequate explanation for cause of death.

In most cases in group B there was a positive bacteriological or virological isolation but with no histological evidence of even minor infection. The classification B was used to show the presence of some positive finding, thus distinguishing the group from group C, which had no positive finding.

## Results

**General factors.** The greatest difference between any two groups in the proportion of homes that had no visit was found between groups A and AB, but the difference was not significant ($p=0{\cdot}197$, Fisher's test of exact probability).

The social status of the family was determined by the occupation of the father, using the Office of Population Censuses and Surveys' Classification of Occupations.[7] The only significant result obtained was that produced by a $\chi^2$ test applied to groups B and C ($\chi^2=7{\cdot}29$, df=2, $p<0{\cdot}05$). The most pronounced differences were in social classes one and two (19% of group B and 34% of group C) and in social class three (44% of group B and 34% of group C).

The family doctor, health visitor, and interviewer made an independent assessment of each family as regards parental supervision and management of the infant's feeding. The state of repair of the house and furnishings were also evaluated. Analysis of the gradings (good, average, or poor) produced a non-significant value for F of 1·57 (df=3 and 342). Almost all estimates (98%) were average or good.

**Maternal factors.** Analysis of the mothers' ages at the birth of the infants showed no significant differences between groups (F=2·90, df=3 and 353). There were also no significant differences between groups when mothers aged under 20 were compared ($\chi^2=2{\cdot}00$, df=3), the percentage of these young mothers in the groups ranging from 9% in group AB to 19% in group A.

Over half (53%) of the mothers smoked. The highest percentage of smokers was in group AB (58%) and the lowest in group C (50%), but the differences were not significant ($\chi^2=0{\cdot}79$, df=3).

Comparison of small for gestational age births[8] in each group among smoking and non-smoking mothers produced a non-significant result ($\chi^2=5·22$, df=3). Similarly, no significant difference was found when the infant was both small for gestational age and below the 10th centile at death ($\chi^2=0·10$, df=1)

After the first born infants had been omitted the number born more or less than 16 months since the mother's last live birth were compared between groups. The only significant result was that 37% of group A had an interval of less than 16 months compared with 14% of group B ($\chi^2=5·77$, df=1, $p<0·05$).

Most mothers (76·3%) had booked with their own doctor or at the maternity hospital by 12 weeks' gestation, with the highest percentage not booking by this time in group A (33%) and the lowest in group C (18%). The differences in booking times were not significant ($\chi^2=3·976$, df=3).

Differences between the groups were small and non-significant ($\chi^2=0·32$, df=3) when antenatal complications were analysed, complications being present in 51% of group AB, 48% of group C, 48% of group B, and 46% of group A.

**Infant factors.** Group A contained the highest percentage (38%) of first born infants compared with 19% in group AB and 27% in group C. Proportions of second born infants were similar in groups AB, B, and C (57, 46, and 44%, respectively), with the lowest representation in A (31%). The highest representation of boys was in group C (66%) and the lowest in group A (50%), but these differences were not significant ($\chi^2=2·56$, df=3)

The mean duration of gestation for the four groups ranged from 38·3 weeks (group A) to 38·9 weeks (group B), a non-significant difference by analysis of variance (F=1·39, df=3 and 354).

The mean birth weights ranged from 3154 g (group B) to 3052 g (group AB), but the difference was not significant by analysis of variance (F=0·32, df=3 and 349). Birth weights ≤1500 g represented from 1·1% of group B to 3·8% of group A The largest number of small for gestational age infants was in group AB (23%) and the smallest in group C (13%). The difference was not significant ($\chi^2=3·64$, df=3).

Differences for mean (SD) crown to heel length were small and not significant (analysis of variance, F=0·34, df=3 and 288), the shortest being 49·65, (3·43) cm (group AB) and the longest 50·40 (3·43) cm (group A).

**Infant's health.** Thirty per cent of group AB, 16% of group B, 15% of group C, and 12% of group A were admitted to the special baby unit some time after birth. Differences were not significant ($\chi^2=7·168$, df=3). Fewer infants in groups A and AB (15% and 4%, respectively) were reported as healthy than in groups B and C (21% in both groups), the differences reaching significance ($\chi^2=9·17$, df=3, $p<0·05$).

Infants in group A were admitted to hospital twice as much as infants in groups B and C, but this was not significant ($\chi^2=6·43$, df=3).

When groups A and AB were compared with groups B and C about the health of the infants 48 hours before death significant differences were obtained. The percentage (69%) of group A who were not healthy was significantly higher than group B (40%) ($\chi^2=8·03$, df=1, $p<0·01$) and group C (30%) ($\chi^2=12·73$, df=1, $p<0·001$). Similarly, the percentage of group AB who were not healthy (60%) was significantly higher than group B ($\chi^2=7·07$, df=1, $p<0·001$) and group C ($\chi^2=12·25$, df=1, $p<0·001$).

**Factors at death.** Mean (SD) age at death was lowest in group C (16·3 (13·2) weeks), highest in group AB (25·3 (20·9) weeks), and for group A was 22·0 (20·8) weeks and for group B was 18·1, (14·0) weeks). As there were significant differences between these means when analysed by an F test (F 4·28, df=3 and 354, $p<0·05$) a Scheffé test was employed to determine where these differences were. At death group AB was significantly older than both group B and group C ($p<0·05$ in both cases) and group A was significantly older than group B ($p<0·01$).

More infants died in the coldest months (40% in December, January, and February). The number of deaths in these months within the groups ranged from 46% in group A to 34% in group C, but these differences were not significant ($\chi^2=1·99$, df=6)

The type of feeding at time of death showed a range for breast feeding alone from 31% (group A) to 13% (group AB) and for bottle feeding alone from 62% (group B) to 49% (group C). Significantly more infants were bottle fed in group B than in group C ($\chi^2=4·01$, df=1, $p<0·05$).

The mean interval from finding the infant dead to the time of postmortem examination for all cases was 38·9 hours. Infants below the 10th centile on weight for age tables employed in hospitals where the postmortem examinations were performed comprised 52% of group A, 42% of group AB, 26% of group B, and 29% of group C. The difference between the groups was significant ($\chi^2=9·93$, df=3, $p<0·05$).

For the crown to heel measure, allowance was made for age by constructing T scores based on local norms for each age group. A non-significant result (F=1·56, df=3 and 272) was obtained.

## Discussion

Previous studies have shown that there are few, if any, differences between cases certified as sudden infant death syndrome and other cases reported to the coroner or procurator fiscal as unexpected deaths.[9-13] Our study, which has found few significant differences between the groups based on degree of information, agrees with this.

Some features commonly associated with sudden infant death syndrome—namely, temporal variation, age distribution, and slight male predominance—were seen in our groups, but in contrast with most previous studies, there was no over representation of SIDS among families towards the lower end of the social class scale. The group as a whole was not marked by social deprivation, poor mothering, or less privileged families.

All infants in the study were reported as dying suddenly and unexpectedly. Classification took place only after postmortem examination and histological analysis. The present data indicated non-pathological differences between the groups, some of which may have been predicted, perhaps being an artefact of the criteria employed in classification—for example, the pattern of incidence of reported ill health just before death in groups A and AB.

Group A, because death was sudden and unexpected by history, could only match the adopted definition in that respect as a cause of death was found. For this reason they could not be classified as SIDS. This group produced the highest proportion of the main epidemiological factors associated with SIDS, thus supporting the finding that these variables are also associated with an increased incidence of all infant deaths.[14]

Most of the evidence for the influence of those variables commonly associated with increased risk of sudden infant death was found in groups A and AB (Fig. 1). It has been well documented that children with conditions such as hypernatraemic dehydration and malnutrition are liable to come from homes where there is a considerable amount of substandard care,[6 15 16] but as there were only two such cases in our study it was considered that these did not introduce a selection bias.

These two groups (A and AB) also included a comparatively high representation of infants whose weight at postmortem examination fell below the 10th centile (Fig. 2). This may be partly due to postmortem dehydration, but as there was no longer or shorter death/necropsy interval between all the groups the presence of an underlying disease process may account for this finding. It has been suggested that growth patterns of some SIDS victims may be similar to those attributed to smoking during pregnancy.[17] Our data, which showed no significant difference between groups as regards maternal smoking, small for gestational age infants, and those who fell below the 10th centile, do not support this theory.

For purposes of certification of death in group AB it may be more practicable to adopt the practice used in Sheffield, in which double registration enables a disease process to be identified and the death also to be described as SIDS.[18] Like a previous study,[19] we had reservations about including these subjects (group AB) in a 'true' SIDS group. Because of the element of doubt we decided, for the sake of the validity of the study, to form a separate group for these cases.

This group would match most closely 'Category B' as defined by Taylor and Emery,[18] where factors

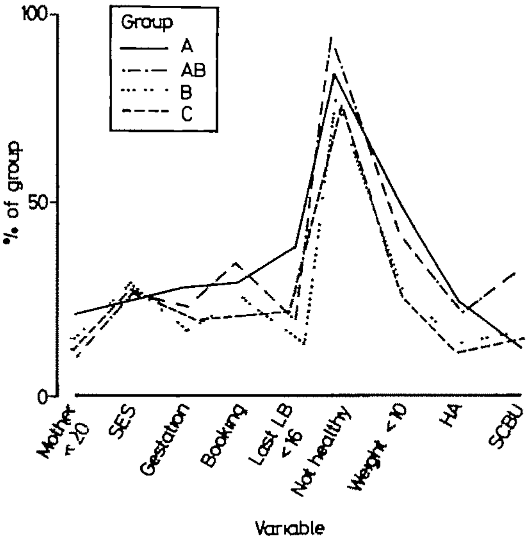

Fig. 1 *Influence of variables commonly associated with increased risk of sudden infant death in the four groups (group A=cases where a definite cause of death was ascertained (n=26), group AB=cases where an associated disorder was detected that may have been implicated (n=53), group B=cases where an associated disorder was detected but not implicated (n=193), group C=cases where no observable associated disorder was present (n=86)) Variables, reading left to right, are Mother <20 years, socioeconomic state (SES), gestation <37 weeks (Gestation), booking time (at hospital) <3 months (Booking), last live birth <16 months ago (Last LB <16), infant not healthy, weight at postmortem examination <10th centile (Weight <10th), number of admissions to hospital (HA), and admissions to special care baby unit (SCBU) Values are percentage of those in group with that variable*

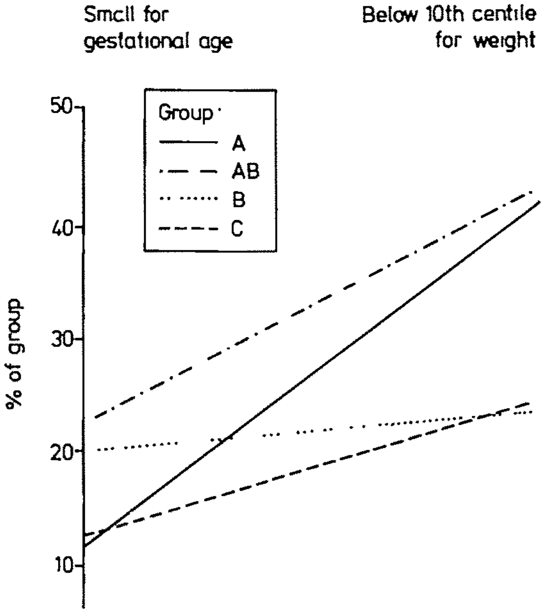

Fig 2 *Percentages of infants from the four groups (group A=cases where a definite cause of death was ascertained (n=26), group AB=cases where an associated disorder was detected that may have been implicated (n=53), group B=cases where an associated disorder was detected but not implicated (n=193), group C=cases where no observable associated disorder was present (n=86)) who were small for gestational age at birth and whose weight at postmortem examination fell below the 10th centile.*

were found that were 'possibly treatable'. Death may have been preventable in some cases in group AB where it was possibly the result of an inappropriate response to infant illness by the caregiver or medical attendant [6] The inclusion and identification of a group 'AB' of this nature in SIDS studies may contribute to understanding the role of conventional paediatric treatment in the reduction of infant mortality.

The finding that there were less bottle fed infants in group C than in group B probably reflected social class, significantly more families from social classes I and II being in group C These two groups were similar for most measures. Some factors commonly associated with SIDS, however, were apparent (second borns, age at death, and winter peaks) and in agreement with the findings in another study[20] support for most attributed influences, such as high incidence of mothers aged less than 20, short interpregnancy intervals, and premature birth, was not forthcoming. From these results it may be concluded that these 'true' SIDS infants would not appear as an 'at risk' population.

In Sheffield, where attempts have been made to identify infants at risk from unexpected death, the proportion of high and low risk infants varied considerably in different 'causal groups' [21] Comparison of this study with ours is difficult due to differences in classification, but there was a similar absence of 'risk' factors in the unexplained groups.

Compared with other infant deaths in Scotland, deaths due to SIDS are not significantly different when analysed by sex of child, social class of father, and age of mother [22] Our study supports Sunderland's view that all infants who die suddenly and unexpectedly are not always cases of SIDS.[23] Many published reports on SIDS are confused by variation in definition. The term 'cot death' is often employed rather than SIDS but in fact only refers to the mode of death—that is, dying unexpectedly and suddenly.[13]

Bergman's definition[1] was created to encompass those deaths that were sudden and unexpected and in which adequate cause had not been established To date, we believe that this definition has not been bettered, even though it may be reconsidered as recommended in a recent report[6] as it does not describe consistently the degree to which the death was unexplained

The diagnosis of SIDS is one of exclusion of recognisable causes of death. Perhaps it should also include the consideration of adverse circumstances surrounding the death in the manner described by Bass *et al*, where fuller investigations into the circumstances surrounding death in 24 cases of certified SIDS changed the diagnosis in all instances.[24] In the present study the circumstances surrounding death were fully investigated, by the police, before postmortem examination, and it is considered that the classification employed has permitted a group of 'true' SIDS to be identified (groups B and C), a group that also rigorously matched the standard definition of the syndrome set out above. The importance of a postmortem examination with prior and subsequent investigations provides a more reliable estimate of the incidence of SIDS. In areas where diagnosis is only made clinically—that is, where there is no autopsy—there may be over reporting or under reporting of the syndrome An accurate diagnosis is beneficial in counselling bereaved parents and in the management of families who have or wish to have subsequent children, particularly about the question of the recurrence risk for SIDS and the use of apnoea monitors

The diagnosis of SIDS may too often provide an 'umbrella' to cover cases where although death may have been sudden and unexpected, it was not always totally unexplained

In studies of sudden infant death there is often concern about the question of infanticide The Infanticide Act does not apply in Scotland. Were there to be a charge it would almost certainly be that of culpable homicide.[25] In the present study only two instances had some suspicion of parental mishandling

'True' SIDS remains the largest single cause of death in infants who die suddenly and unexpectedly. Until a diagnostic marker or markers have been identified and agreed on, the diagnosis of SIDS remains dependent on the judgment of the pathologist. Misdiagnosis serves to confuse those seeking the cause(s) of these tragic deaths. This may give a falsely inflated picture of the incidence of the syndrome and also produce an unnecessarily high level of anxiety among parents.

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## *Short reports*

# Pulse oximetry in preterm infants

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SUMMARY One hundred and twenty five measurements of arterial oxygen saturation ($Stcao_2$) obtained with a transcutaneous pulse oximeter were compared with direct arterial oxygen tension ($Pao_2$) in 13 preterm infants with predominantly fetal haemoglobin. $Stcao_2$ of 86–92% corresponded to $Pao_2$ of 5–13 kPa. $Stcao_2$ above 92%, however, was sometimes associated with $Pao_2$ above 13 kPa.

Non-invasive techniques for monitoring blood gas tensions in neonates have been used over the past two decades, but some transcutaneous sensors of arterial oxygen tension have been found unreliable clinically.[1] Recent skin sensors for continuous monitoring of arterial oxygen saturation ($Stcao_2$) based on pulse oximetry have been evaluated in patients with predominantly adult haemoglobin and found to be easy to use, to be accurate, and to have no risk to the patient.[2] Little is known about the performance of the pulse oximeter in preterm infants with predominantly fetal haemoglobin.

As oxygen treatment of preterm infants has been regulated by arterial oxygen tension rather than saturation in the past it is important for clinicians to have data comparing results using the pulse oximeter with arterial $Po_2$. This study compared $Stcao_2$ and $Pao_2$ in preterm infants less than 48 hours old who had not received any adult blood.

## Patients and methods

Preterm infants admitted to the neonatal intensive care unit were included if they were less than 48 hours old and had not had any blood transfusions, thus ensuring over 70% fetal haemoglobin concentration,[4] and they had an umbilical artery oxygen electrode in the thoracic aorta at the level between the sixth and ninth thoracic vertebrae as part of their management.[3]

For each data recording session the umbilical artery electrode was calibrated using an umbilical arterial blood sample in a Radiometer ABL-2 blood gas analyser.

Gestational age, birth weight, postnatal age, haemoglobin concentration, arterial blood pH, skin temperature, blood pressure, pulse rate, arterial carbon dioxide tension ($Paco_2$), and clinical state of each neonate were recorded The ear-lobe clip pulse oximeter sensor was then placed on the hand Paired measurements of $Stcao_2$ and $Pao_2$ were made with a Ohmeda Biox 3700 pulse oximeter and an umbilical arterial oxygen electrode (Biomedical Sensors. High Wycombe, England), respectively, with a minimum of 30 seconds' stabilisation for each reading. The calibration of the umbilical artery electrode was rechecked at the end of the measurements on each neonate. The total blood sampled for each baby was less than 2 ml.

## Results

Thirteen neonates were studied and 125 paired measurements of $Stcao_2$ and $Pao_2$ made. All the neonates were normotensive (mean arterial pressure > 30 mm Hg), and they had heart rates of 130–160/minute and a $Paco_2$ of 3 17–8·07 kPa (mean 6·12 kPa). Eight neonates were ventilated for hyaline membrane disease, five were receiving oxygen by headbox, and none of them had jaundice at the time of the study. Their mean oxygen requirement was 0·37 (range 0·24–0·60), and hence right to left ductal shunting was considered unimportant.

The oximeter sensor applied to an oedematous, bruised hand of one neonate who had had a breech delivery gave a poor quality signal. Movement of the arm carrying the oximeter sensor caused destabilisation of the oximeter reading. The table summarises the clinical details on the 13 neonates. The figure shows the 125 paired measurements. Mean (2SD) curves drawn in the figure were fitted with a MINITAB computer program.

$Stcao_2$ of 86–92% corresponded to a range of $Pao_2$ of 5·0–13·0 kPa. $Stcao_2$ of 93%, however, corresponded to a $Pao_2$ of from 8·5 to over 14·0 kPa, and

Table *Clinical data on the 13 preterm infants studied*

| | *Mean* | *Range* |
|---|---|---|
| Gestational age (weeks) | 29 | 26–32 |
| Birth weight (g) | 1324 | 610–2360 |
| Postnatal age (h) | 26·7 | 8·2–47·0 |
| Arterial blood pH | 7·3[illegible] | 7·1[illegible]7–7·440 |
| Haemoglobin concentration (g/l) | 150 | 113–192 |
| Skin temperature (°C) | 36·[illegible] | 36·[illegible]–37·0 |
| Duration of recording per infant (minutes) | 53·59 | 35·4–88·0 |

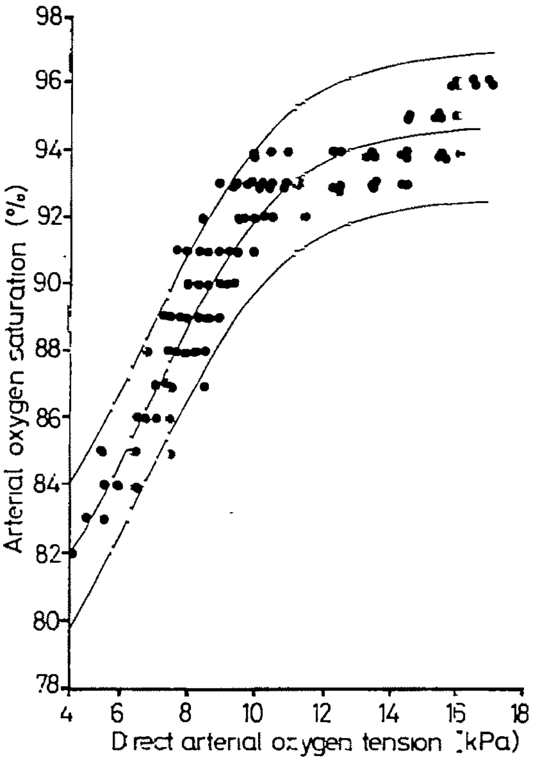

Figure *Comparison of 125 paired measurements of transcutaneous arterial oxygen saturation (StcaO2) and arterial oxygen tension (PaO2). The fitted mean curve ±2SD is shown.*

therefore an Stcao$_2$ of over 92% could be associated with hyperoxia. Stcao$_2$ of 94–95% was associated with a Pao$_2$ of well over 13 kPa.

## Discussion

Sick neonates have such rapidly and widely fluctuating Pao$_2$ that intermittent blood gas measurements are a poor reflection of the changes. An indwelling umbilical artery oxygen electrode, though clinically useful for continuous monitoring of Pao$_2$ in a sick baby, requires special techniques of insertion, and umbilical artery catheterisation in itself is associated with complications.[3] [5] Transcutaneous sensors have been reported not only to be unreliable if the baby is hypotensive or severely acidotic or anaemic, or when vasodilators are being given—all of which are common in sick preterm neonates—but also to cause burns.[1]

The pulse oximeter is safe and easy to use and does not require calibration.[1] [2] The IL-282 co-oximeter has been shown to overestimate carboxyhaemoglobin concentrations, thus underestimating oxyhaemoglobin concentration in the presence of fetal haemoglobin.[6] This has not been evaluated in pulse oximeters, which use different absorption spectra of light wavelengths, and this could be a source of error in the present study. Our study showed that in preterm infants with predominantly fetal haemoglobin Stcao$_2$ of 86–92% corresponds to a Pao$_2$ of 5·0–13·0 kPa, and an Stcao$_2$ of greater than 92% may be associated with hyperoxia and should be checked with in vitro blood gas analysis. Oedema bruising, and movement at the site of the oximeter sensor can result in inaccurate oximeter readings.

More evaluation of pulse oximetry in different fetal haemoglobin concentrations, underperfusion, and vasoconstrictor drug treatment is needed before it can be widely used in neonatal intensive care. Pulse oximetry, however, can be used to monitor oxygenation in preterm neonates with predominantly fetal haemoglobin. The pulse oximeter's ability to respond rapidly and to display changes in pulse rate make it useful during resuscitation of newborn babies in the delivery room.

We thank Mr Vic Aber for help with the statistics and Miss Tracey Irving for typing the paper. AW was a WHO fellow.

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(See pages 879–81 and 882–8.)

# Seasonal variation of glycosylated haemoglobin

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SUMMARY Retrospective analysis of glycosylated haemoglobin concentrations in a diabetic outpatient clinic over three and a half years showed a small seasonal variation in the mean value with a peak in mid February and a nadir in mid August.

Measurements of glycosylated haemoglobin are commonly used in diabetic clinics to monitor glycaemic control It has been suggested that seasonal fluctuations in concentrations occur[1] and could be of clinical importance. We present a retrospective analysis to determine whether seasonal variations in glycosylated haemoglobin concentrations are detectable in a paediatric diabetic outpatient clinic.

## Patients and methods

Diabetic children and adolescents attending a single paediatric diabetic clinic between December 1982 and June 1986 with a minimum of four estimations of glycosylated haemoglobin concentrations each were studied. Concentrations measured at diagnosis and during admissions for infection and ketoacidosis were excluded A total of 1232 estimations in 125 children were analysed. There was no seasonal variation in frequency of estimations made. The age range of the patients was 0·6 to 19·3 years, and sex distribution was almost equal

Glycosylated haemoglobin concentrations were measured in one laboratory by an ion exchange column method for total haemoglobin $A_1$ (Hb$A_1$) with a borate eliminator for aldimine reversible material in a thermostatically controlled environment.

A mainframe computer was used to analyse the values for each patient by a sophisticated single cosinor program to compute the population mean cosinor using a number weighted mean cosinor analysis.[2]

## Results

The mean (SD) total glycosylated haemoglobin was 9·93% (0·06)%. There was a highly significant ($p < 0{\cdot}001$) seasonal variation (Figure) and the amplitude of oscillation in total glycosylated haemoglobin was 0·34% (95% confidence limits 0·16–0·53%). The acrophase, the time of year at which glycosylated haemoglobin concentrations peak, was 1·47 months—namely, mid February—with 95% confidence limits from early January to mid March, and the nadir occurred at 7·47 months—namely, mid August—with 95% confidence limits from early July to mid September.

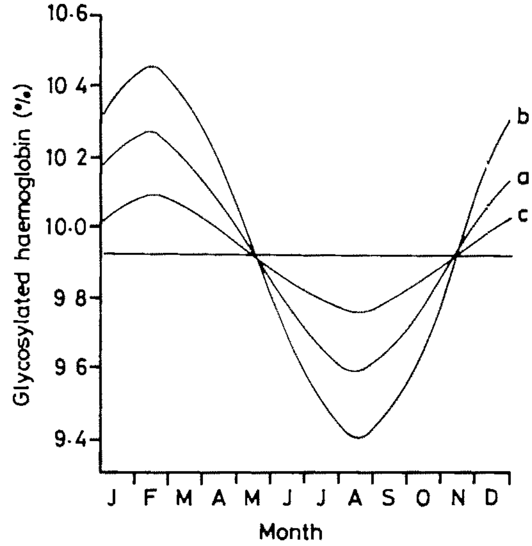

Figure *Seasonal variation in glycosylated haemoglobin concentrations (curve a = line of mean oscillation, curves b and c = 95% confidence limits)*

## Discussion

The seasonal variation in glycosylated haemoglobin concentrations almost certainly reflects similar variations in mean blood glucose concentrations and is unlikely to be artefactual. Glycosylated haemoglobin can be affected by the temperature at which samples are stored and assayed, but seasonal temperature differences would produce changes opposite to those documented here[3]

Physical activity is likely to be greater in the summer because of more daylight hours and milder weather, and this could produce lower glucose concentrations. Viral respiratory infections are more common in winter and worsen glucose control. Similarly, food intake is greater in the winter months when children gain relatively more weight than height. Seasonal variations in hormone concentrations may influence or be influenced by glucose concentrations.[4]

This study was done because of the clinical impression that diabetes was better controlled in the summer, and it is interesting that the mean amplitude of variation detected was small. This probably indicates that some patients have greater and therefore noticeable seasonal fluctuations, and it might be of clinical value to identify such children. This seasonal variation may be accentuated in higher latitudes where greater climatic differences between winter and summer occur

We thank the departments of chemical pathology, and medical illustration Hope Hospital, Salford, and Mrs K Cordwell

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# Mitral valve disease in Marfan's syndrome

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SUMMARY Cardiovascular disease in Marfan's syndrome presenting in childhood affects the mitral valve more often than the aortic valve or the aorta, as in adults. Early evaluation of the cardiovascular system is necessary for any child in whom Marfan's syndrome is suspected.

Marfan's syndrome comprises a characteristic phenotype with skeletal, ocular, and cardiovascular disorders. The dissection of the aorta and disorders of the aortic root which usually become apparent during the second and subsequent decades have been described Impairment of the mitral valve is, however, also associated with Marfan's syndrome. Indeed, it is the most common cardiac manifestation in childhood and may present in the first year of life. We report on a child with Marfan's syndrome, which was apparent at birth, who died in early infancy from mitral valve disease. Early specialist evaluation of the cardiovascular system is essential in all cases of Marfan's syndrome.

## Case report

The patient was the third child of unrelated white parents, with no family history to suggest Marfan's syndrome. Both siblings were well, the first having a ventricular septal defect that had closed spontaneously. After a spontaneous labour at term delivery was vertex vaginal; birth weight was 4040 g (90th percentile), length 54·5 cm (0·7 cm above the 97th percentile), and occipitofrontal circumference 35·5 cm (90th percentile). Several abnormalities were apparent: the baby seemed abnormally long and slim with little subcutaneous fat; there was obvious arachnodactyly of both feet and hands (middle finger length 4 cm (97th percentile); metacarpal length was 1·9 cm (excluding the epiphysis; metacarpal index 8·25)) and span 57 cm (2·5 cm >length): she had a long thin face and sparse hair; the fingers and toes were hyperextensible; there was ulnar deviation of both hands and limitation of extension of both elbows and knees as well as pectus carinatum with prominence of the right side of the chest and divarication of the recti; and she had a high arched palate. A soft systolic murmur was audible at the first examination but subsequently disappeared.

Investigations in the neonatal period included chest radiography, electrocardiography, chromosome analysis, and estimation of plasma and urinary amino acid concentrations; all yielded normal results, except that the *x*-ray pictures showed the arachnodactyly. She was discharged home, being bottle fed, on the fourth day and followed up in the baby clinic at 7 and 12 weeks of age, when her

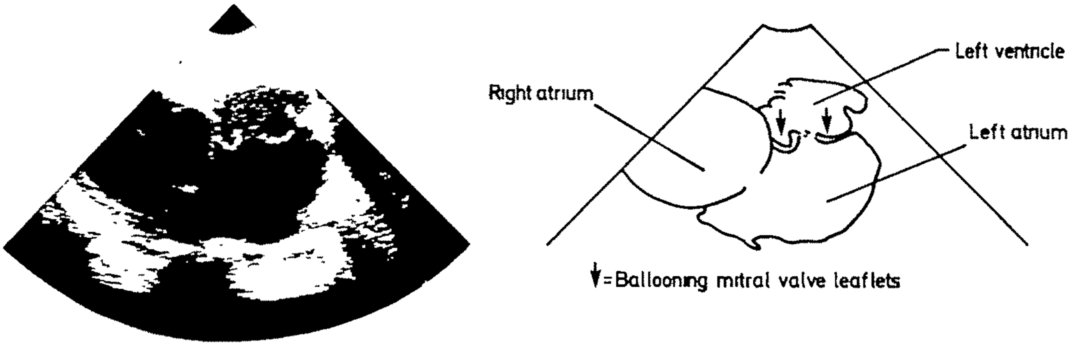

Figure *Echocardiogram (foreshortened subcostal view) showing dilated left and right atria (LA, RA) and mitral leaflets billowing back into left atrium (arrowed)*

developmental progress was normal Her weight gain was suboptimal, however, falling from the 90th percentile at birth to just below the 50th percentile at 12 weeks. Rate of growth for length and occipitofrontal circumference were normal. At the 12 week visit the soft systolic murmur was heard again.

At 16 weeks of age she was admitted severely ill with a two day history of fever, irritability, and tachypnoea She had peripheral circulatory failure, central cyanosis, an active precordium with prominent ventricular impulses, and a loud systolic murmur; the liver could be felt 4 cm below the costal margin, and there were signs of left basal pneumonia. A chest *x*-ray film showed a large boot shaped heart with patchy shadowing in the right middle and left lower lobes. An electrocardiogram showed an axis of +135° and right ventricular hypertrophy. Four hours after admission she collapsed after a convulsion and required intravenous fluid replacement and assisted ventilation

An echocardiogram showed floppy prolapsing anterior and posterior mitral leaflets with a dilated valve ring (figure) All four chambers were dilated, as were the great vessels; injection of contrast showed severe tricuspid regurgitation, Full inotropic support was given together with diuretics and mannitol for oliguria. Asystole occurred 40 hours after admission, and she could not be resuscitated. Permission for necropsy was refused The immediate family were subsequently screened; none had any suggestion of Marfan's syndrome or cardiac disease.

## Discussion

In 1896 Marfan described a skeletal abnormality in a 5 year old girl characterised by abnormally long, slender extremities. The term arachnodactyly was suggested by Archard about six years later. Ironically, subsequent experience has cast doubt on whether this case was what we would today consider to be Marfan's syndrome with the characteristic phenotype and involvement of the skeletal, ophthalmological, and cardiovascular systems.[1] The syndrome is inherited in an autosomal dominant manner with variable expression, although about 15% of cases seem to be new mutations,[2] as this case.

Although the presentation of Marfan's syndrome in adults, with aortic dilatation, incompetence, or dissection, is well known, few paediatric text books make the point that in children and young adults with the disease mitral valve abnormalities are found more commonly than aortic lesions. Indeed, the most commonly used reference book about malformations fails even to mention that mitral valve disease may occur Marfan's syndrome is rarely diagnosed in young children, and its full import needs to be emphasised.

Up to 61% of children with overt Marfan's syndrome may have appreciable heart disease In one series of 36 children 12 girls and five boys had mitral regurgitation alone, three boys had mixed mitral and aortic regurgitation, and one boy had aortic regurgitation alone [3] The aorta, aortic valve, sinuses of Valsalva, pulmonary artery, and mitral valve may all be affected [3 4] These abnormalities are part of a widespread connective tissue disorder affecting many organs. Although there may be accelerated linear growth in childhood, children with severe heart disease may fail to thrive. The gross signs in our patient may have implied more severe disease, and the failure to gain weight may have indicated severe cardiac disease.

Disease affecting the mitral valve is usually more benign than that of the aortic valve, but, rarely, acute emergencies may result from rupture of the chordae tendinae,[5] bacterial endocarditis,[6] or cardiac failure precipitated by intercurrent infection, as in the patient reported on here Surgical treatment for the floppy mitral valve abnormalities comprises repair or replacement of the valve. In young infants either of these carries a high risk and the results are disappointing.[3 5]

This report draws attention to the importance of careful assessment of the cardiovascular state of any child suspected of having Marfan's syndrome This patient died after an acute illness with gross cardiac failure due to valve disease, presumably precipitated by an intercurrent respiratory infection. Early evaluation of the cardiovascular system might have resulted in earlier and possibly successful intervention.

We thank Dr EME Poskitt and Dr M Bini for permission to report on their patient

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# Bacterial tracheitis in Down's syndrome

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SUMMARY Four children with Down's syndrome and bacterial tracheitis are described. In three the infection was due to *Haemophilus influenzae.* In patients with Down's syndrome presenting with stridor tracheitis should be considered and appropriate treatment started.

Bacterial tracheitis (pseudomembranous croup) is characterised by upper airways obstruction with fever and is diagnosed by the presence on bronchoscopy of purulent tracheal secretions and a normal epiglottis. Most cases are due to *Staphylococcus aureus,* but *Haemophilus influenzae* and various streptococci have also been implicated.[1–4] Sofer *et al* reviewed 332 children with infective upper airways obstruction; 297 (89%) had croup, 28 (8%) epiglottitis, and 7 (2%) bacterial tracheitis.[2]

We report four children with Down's syndrome seen over three years with severe airways obstruction due to tracheitis. All were previously well and none had congenital heart disease In three, *H influenzae* was identified as the causative organism. Over the same period 206 children were seen with croup, and two with epiglottitis. None of them had Down's syndrome, nor was bacterial tracheitis diagnosed in any other child

## Case reports

**Case 1.** A 10 year old boy presented with a 24 hour history of cough, and a three hour history of increasing stridor. He was distressed, feverish, had a marked stridor, and showed signs of severe repiratory obstruction. Urgent bronchoscopy showed that the epiglottis was not enlarged and the larynx only slightly inflamed. The trachea was hyperaemic and oedematous, and copious mucopus was seen, which subsequently grew *H. influenzae.* Tracheal intubation relieved the obstruction and he breathed spontaneously. He was treated with ampicillin and flucloxicillin, tracheal aspiration, and physiotherapy. By the next day there was widespread consolidation of the lungs and enlargement of the mediastinum. His condition deteriorated and two days later ventilation was required. The antibiotics were changed to chloramphenicol and cefotaxime. With suction, tracheal lavage, and physiotherapy he gradually improved. He was extubated after seven days, and discharged well two days later.

**Case 2.** A 2½ year old boy was admitted with a six day history of measles. He had conjunctivitis, Koplik's spots, a morbilliform rash, cough, and mild stridor but no dyspnoea or recession Three days after admission, over two to three hours he became increasingly dyspnoeic with severe respiratory obstruction. Bronchoscopy showed a normal epiglottis and larynx and a narrowed oedematous upper trachea with a membrane and copious pus, *H influenzae* was grown from the pus. He was intubated, ventilated, and given cefotaxime. The endotracheal tube became blocked repeatedly with secretions, and he developed extensive bilateral consolidation. With suction and vigorous physiotherapy he gradually improved. He was extubated seven days after admission and discharged well on the thirteenth day.

**Case 3.** A 5 year old girl had a cough for six weeks which did not respond to erythromycin. A chest radiograph showed collapse and consolidation of the right lower lobe. Treatment was changed to ampicillin and flucloxacillin, together with physiotherapy. Three weeks later the radiological appearances were unchanged, so she was admitted for bronchoscopy. There were thick yellow secretions in the trachea and both main bronchi These were aspirated and generalised hyperaemia was seen, and *H. influenzae* was grown from them

Twelve hours after bronchoscopy she developed severe stridor and rapidly worsening airways obstruction. Laryngoscopy showed oedematous cords and copious tenacious secretions in the trachea She was intubated, given chloramphenicol, and regular tracheal toilet was carried out. For 24 hours the secretions remained thick and profuse, but lessened thereafter. She was extubated after three days and discharged after one week.

**Case 4.** A girl aged 17 months was admitted with a 12 hour history of cough and increasing dyspnoea. Erythromycin had already been started. She was feverish, with stridor and moderate respiratory obstruction. A chest radiograph was normal. Over two hours she deteriorated rapidly, becoming distressed and cyanosed. At bronchoscopy the epiglottis was normal, there was slight oedema of the vocal cords, and the trachea was oedematous, inflamed, and contained a lot of pus. This showed Gram positive cocci on microscopy, but was sterile on culture. She was intubated and given penicillin, flucloxacillin, and chloramphenicol Copious secretions were aspirated from the tube. Patchy areas of consolidation were seen on subsequent *x* ray pictures. After nine days she was sufficiently improved for a trial of extubation. Initially she seemed satisfactory but 10 hours later had a cardiorespiratory arrest. She was immediately reintubated and resuscitated, but remained hypotonic and unresponsive and required assisted ventilation Within 24 hours there was some improvement in her neurological state. She was successfully extubated three days later but remained severely handicapped with intellectual deficit and weakness of all four limbs.

## Discussion

We have described four children with Down's syndrome and purulent tracheitis. In three *H influenzae* was the causative organism. No bacteria were cultured from the fourth patient, who had received an antibiotic, but the presentation and findings were otherwise characteristic of bacterial tracheitis

The clinical presentation was similar to that in previously reported cases;[1-4] the children had higher temperatures, worse respiratory obstruction, and were more unwell and toxic than is usual in croup. All required urgent intubation, which permitted definitive diagnosis. All produced copious secretions requiring intensive physiotherapy, suction, and lavage One child suffered a cardiorespiratory arrest, a common complication of bacterial tracheitis.[1-3]

Our cases show a striking association between Down's syndrome and bacterial tracheitis; one child described by Liston *et al* also had Down's syndrome.[3] Interestingly, in three of our children *H. influenzae* was the causative organism; it has not been common in other series.[1-4]

Bacterial tracheitis should be considered when a child with Down's syndrome presents with upper airways obstruction. Tracheitis requires urgent bronchoscopy and intubation, and patients should be cared for in a unit with adequate facilities for managing this life threatening condition.

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964 *Archives of Disease in Childhood*, 1987, **62**

# Penicillin resistant pneumococcal peritonitis in nephrotic syndrome

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SUMMARY Two infants with nephrotic syndrome who developed penicillin resistant pneumococcal peritonitis while receiving penicillin chemoprophylaxis are reported and the problems associated with prophylaxis against pneumococcal infection discussed. It is suggested that penicillin prophylaxis may be hazardous in an environment in which penicillin resistant pneumococci are prevalent

Children with nephrotic syndrome are at an increased risk of developing peritonitis due to *Streptococcus pneumoniae*. The depressed immune state caused by the nephrotic syndrome is due to decreased serum concentrations of immunoglobulins[1] and impaired opsonisation,[2] cellular immunity,[3] and granulocyte chemotaxis.[2] Prophylaxis against pneumococcal infection may be attempted with pneumococcal polysaccharide vaccine or with oral penicillin We report two children with nephrotic syndrome who developed penicillin resistant pneumococcal peritonitis while receiving prophylaxis with oral penicillin. *S pneumoniae* was identified as an α-haemolytic streptococcus sensitive to optochin. Antibiotic sensitivity testing of this organism was performed on 5% sheep blood agar by the Kirby-Bauer disc diffusion method. Penicillin resistance was defined by a zone of inhibition smaller than 20 mm around a 5 μg methicillin disc.

## Case reports

### CASE 1

A 2 month old black boy with histologically confirmed Finnish type congenital nephrotic syndrome was given oral prophylaxis with phenoxymethyl penicillin (62·5 mg twice daily) and co-trimoxazole (2 mg/kg daily of trimethoprim). One week after discharge he was readmitted with vomiting and abdominal distension. Examination showed that his systolic blood pressure was 40 mm Hg and pulse rate was 120/minute. He had poor peripheral perfusion and generalised oedema. Abdominal examination showed ascites, and the liver and spleen edges were palpable 2·5 cm and 1 cm, respectively, below the right and left costal margins. The heart was normal and the lung fields were dull to percussion at both bases There was neck retraction, a bulging anterior fontanelle, and hypertonia.

Laboratory investigations showed a haemoglobin concentration of 7·7 g/dl, a white cell count of $8\cdot2 \times 10^9$/l, and a platelet count $412 \times 10^9$/l, serum urea concentration was 17·8 mmol/l, sodium concentration 137 mmol/l, potassium concentration 4·0 mmol/l, chloride concentration 99 mmol/l, and creatinine concentration 145 μmol/l (normal for age, 30–55 μmol/l). Examination of the cerebrospinal fluid was normal. *S pneumoniae* resistant to penicillin was cultured from the peritoneal fluid. He was treated with intravenous fluid replacement and albumin together with frusemide and cefotaxime. He died two days after admission.

### CASE 2

A 2 day old black girl was admitted after a generalised seizure. She was the product of an uneventful pregnancy and delivery. On examination her rectal temperature was 34·8°C, she had sclerema of the limbs, and Kussmaul's respiration. The pulses were all present, with a rate of 160/minute. The heart and lungs were normal on auscultation. On abdominal examination the liver edge was palpable 4 cm below the right costal margin. The child had generalised hypertonia and a tense fontanelle.

Laboratory investigations showed a haemoglobin concentration of 14·2 g/dl, a white cell count of $7\cdot9 \times 10^9$/l, and a platelet count of $125 \times 10^9$/l. Her serum sodium concentration was 126 mmol/l, potassium concentration 7·5 mmol/l, chloride concentration 98 mmol/l, bicarbonate concentration 12·3 mmol/l, urea concentration 22·9 mmol/l, and creatinine concentration 268 μmol/l (normal for age, 60–75 μmol/l). Analysis of urine by dipstick showed a pH of 5, moderate proteinuria, and haematuria. The fractional excretion of sodium on admission was 0·34%, suggesting hypovolaemia. Treatment was started with intravenous fluid replacement and sodium bicarbonate, together with penicillin and cefotaxime. She subsequently improved but became progressively more oedematous and developed ascites. The serum albumin concentration decreased from 19·1 g/l on admission to 8 g/l, with severe proteinuria on testing of the urine The serum cholesterol concentration was 5·2 mmol/l (normal for age 1·8–4·5 mmol/l) and triglyceride concentration 1·48 mmol/l (normal for age 0·37–1·2 mmol/l) The nephrotic syndrome was diagnosed and studies to determine the aetiology were planned. The antimicrobial treatment was changed to phenoxymethyl penicillin (62·5 mg twice daily) and cotrimoxazole (2 mg/kg daily of trimethoprim). Two weeks later she developed tense ascites, pallor, and hypothermia. Culture of the peritoneal fluid showed *S pneumoniae* resistant to penicillin She improved on treatment with intravenous vancomycin.

## Discussion

Patients with the nephrotic syndrome are at an increased risk of developing systemic pneumococcal infections due to perturbations of the normal immune responses.[1-3] Immunisation with pneumococcal polysaccharide vaccine seems to be the most rational method of preventing pneumococcal disease, but it may not be effective in children younger than 2 years,[4] or protective in patients with nephrotic syndrome who are resistant to steroid treatment.[5] For these reasons we have used penicillin prophylaxis in nephrotic children younger than 2 years of age which has the potential disadvantage of encouraging the emergence of penicillin resistant pneumococci

In a recent survey at this hospital 24% of pneumococcal isolates from blood culture in children were due to penicillin resistant strains that were both hospital and community acquired.[6] We believe that the two patients reported here became colonised in the nasopharynx with penicillin resistant pneumococci while they were in hospital, and that the use of prophylactic penicillin selected for penicillin resistant strains subsequently resulted in invasive disease. Our experience suggests that this practice may be hazardous in a hospital or community in which penicillin resistant pneumococci are common. Our current practice is to give pneumococcal vaccination to nephrotic children at 2 years of age. For younger children we no longer give antimicrobial prophylaxis but explain the potential risks of infection to the parents who are advised to seek urgent medical attention for any febrile illness. Further studies are planned to evaluate the role of antimicrobial prophylaxis in preventing pneumococcal infection in nephrotic syndrome.

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# Infant feeding and atopy

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SUMMARY Parents of 457 5 year olds from a previous study of infant feeding and eczema in the first year of life were questioned about subsequent atopy. No association was found with early breast or bottle feeding. Family history was important. Parental recall of first year eczema was often inaccurate.

Between 1979 and 1981 we studied the association between different types of infant feeding and eczema [1] Four hundred and seventy five infants born to parents with a family history of atopy were investigated to see if there was an association between feeding in the first weeks of life and the incidence of eczema during the first year. Exclusive breast feeding in the first four weeks postponed the onset of eczema; significantly fewer infants had eczema at three and six months, but by one year the incidence was similar in breast and bottle fed infants. To investigate a possible association with asthma these infants were followed up on their fifth birthdays.

## Subjects and methods

Two months before each child's fifth birthday the parents of the 475 children were contacted by letter. Questionnaires were then sent two weeks before the fifth birthday. Questions were asked about the presence of skin diseases (including eczema since birth) and respiratory problems (including wheeze and asthma) diagnosed by a doctor.

Parents who did not reply were sent a second questionnaire. If this failed they were either visited or telephoned. When parents had moved and their new address was unknown, the help of health visitors, family practitioner committees, and the school health service was enlisted.

The significance of differences between proportions was analysed using the $\chi^2$ test.

## *Results*

Replies were received from 457 (96%) of the 475 parents.

### ASTHMA

Ninety one children (20%) were reported to have had a wheezing attack between 1 and 5 years of age, and 45 (10%) were diagnosed by a doctor as having asthma. Of these 45, 28 (62%) were boys and 17 (38%) were girls. Seventeen had been seen in hospital because of their asthma and eight had been treated as inpatients. At the time of the survey 26 were still said to have asthma. Eczema was diagnosed at some time in 23 (50%) of these 45 children, and 10 still had eczema at the age of 5.

Table 1 shows the association between infant feeding and risk of developing asthma: there were no significant differences.

In the earlier study the family history of atopy was defined as either 'mild' (one parent with either eczema or asthma) or 'severe' (either both parents affected, or one parent with both eczema and asthma). Of the 45 children who had been diagnosed as having asthma, 18 (40%) had a family history of 'severe' atopy compared with 81 (20%) of the 408 children who were not diagnosed as having asthma ($p < 0{\cdot}01$).

### ECZEMA

Between their first and fifth birthdays, 39 children who had not had eczema in the first year of life were reported to have had eczema diagnosed by a doctor. In the previous study 181 children were identified who had eczema in the first year of life; of these 174 appeared in the five year follow up. Thus 213 children either had had eczema diagnosed by the survey team in the first year of life or were reported to have developed eczema subsequently; 113 (53%) were male and 100 (47%) female. Forty children (9% of 457) still had eczema at the age of 5.

The association between early feeding and eczema during the first 5 years is shown in Table 2; there were no significant differences. Of the 213 children reported to have had eczema, 59 (28%) had a family history of 'severe' atopy, compared with 40 (16%) of the 244 children not reported to have had eczema. The association with family history was significant ($p < 0{\cdot}01$).

This follow up was used to test the accuracy of parental recall of their child's eczema. Parents were asked when the child was 5 years old whether eczema had been diagnosed in the first year. Four hundred and fifty five replied: 360 said 'no', and of these, 109 (30%) had documented evidence of eczema under the age of 1 year. Ninety five said 'yes'; of these, 15 (16%) had no documented evidence of eczema.

Table 1 *Association between feeding during the first four weeks and the incidence of asthma in the first five years*

| *Type of feed* | *No** | *Patients with asthma No (%)* |
|---|---|---|
| Breast milk only | 217 | 19 (8·8) |
| Breast milk/or soya milk, or both | 86 | 11 (12·8) |
| Cows' milk only | 150 | 15 (10·0) |
| Total | 453 | 45 (9·9) |

*Excludes one breast fed and three fed cows' milk in whom the diagnosis of asthma was unknown

Table 2 *Association between feeding during the first four weeks and the incidence of eczema in the first five years*

| *Type of feed* | *No** | *Patients with eczema No (%)* |
|---|---|---|
| Breast milk only | 217 | 103 (47·5) |
| Breast milk/or soya milk, or both | 86 | 38 (44·2) |
| Cows' milk only | 152 | 72 (47·4) |
| Total | 455 | 213 (46·8) |

*Excludes one breast fed and one fed cows' milk in whom the diagnosis of eczema was unknown

## Discussion

The recording of infant feeding patterns in the previous study, which included a dietary diary, was considered to be reliable.[1] Eczema in the first year was also carefully defined and clinical assessment made by one doctor. In the follow up there was no reason to think that biases had arisen due, for example, to differential recall of asthma or eczema between 1 and 5 years of age by parents of children who received breast or bottle feeds in the first 4 weeks. The high response rate made it unlikely that biases could be the result of differential drop out rates

No evidence was found for an association between type of feeding and development of asthma in the first 5 years There is, however, a significant association between family history of atopy and risk of the child developing asthma by the age of 5

Studies of the aetiology of eczema tend to lack precision in the definition of eczema and accurate recording of the infant's diet. It is worrying that in this motivated and cooperative group of parents with a low drop out rate, recall at five years of eczema during the first year was relatively poor, even though the eczema was diagnosed and discussed with them by a doctor whom they saw regularly. This must have implications for studies relying exclusively on parental recall for evidence of eczema in infancy.

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# Type V hyperlipoproteinaemia in neonates

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SUMMARY A boy investigated for neonatal jaundice was noted to have lipaemic serum and was subsequently shown to have type V hyperlipoproteinaemia. Dietary treatment was maintained for five years and he followed a typical clinical course Circumstantial evidence suggested an autosomal recessive inheritance pattern.

Type V hyperlipoproteinaemia is rare in childhood and has not to our knowledge been described in a neonate. It is often difficult to distinguish between type I and type V hyperlipoproteinaemia, and differentiation usually relies on measuring plasma post-heparin lipoprotein lipase (PHLPL) activity which is deficient in type I hyperlipoproteinaemia and usually normal in type V.[1] Until 1974 there was no accurate method of measuring plasma post-heparin lipoprotein lipase. Since then three children have been reported with definite type V hyperlipoproteinaemia but normal PHLPL activity,[2-3] and there have been several descriptions of children with features suggesting type V hyperlipoproteinaemia[4-6] The youngest reported was 2½ years old [4]

## Case report

A 5 year old boy who had been investigated for neonatal jaundice was found to have lactescent serum when 6 days old. Xanthelasma and eruptive xanthomata (buttocks) subsequently developed. The liver and spleen were not enlarged. Breast feeding was stopped and a feed containing a medium chain triglyceride formula (Pregestimil) was begun The first plasma lipid profile was done when he was 2 months old, when a low fat diet started (table 1). The subsequent clinical course was uncomplicated and at 2 years of age, he began a normal diet A brief recurrence of eruptive xanthomata, however, necessitated a return to restricted long chain triglyceride feeding.

The boy migrated to Australia with his family. When he was 2 years and 7 months old he developed acute pancreatitis. The parents, who controlled his diet carefully, reported no dietary indiscretion before the episode Fasting serum lipid concentrations subsequently remained under control (table 1). Triglyceride concentrations, although never within the normal range, did not exceed 6·4 mmol/l. High density lipoprotein cholesterol (mean 0·41

Table 1 *Fasting plasma lipid profile*

| | Age (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *0·2** | *0·5* | *1* | *2* | *2·7†* | *4* | *5* | *Normal range* |
| Plasma lipids (mmol/l) | | | | | | | | |
| Triglyceride | 18·4 | [illegible] | 12 | 1·4 | 45·1 | 3·1 | 4·9 | 0·1–1·6 |
| Total cholesterol | 3·8 | [illegible] | 1·0 | 2·25 | 10·1 | 2·1 | 4·2 | 3·6–6·2 |
| Lipoprotein electrophoretic pattern (%) | | | | | | | | |
| Alpha | 7 | 1[illegible] | 15 | 6 | 14 | 5 | 6 | 35‡ |
| Pre-Beta | 71 | 2[illegible] | 35 | 3[illegible] | 76¶ | 82¶ | 55 | 15‡ |
| Beta | 13 | 2[illegible] | 30 | 40 | | | 24 | 50‡ |
| Chylomicrons | 9 | 3[illegible] | 20 | 24 | 10 | 13 | 15 | 0‡ |

*Just before start of fat restricted diet, †after pancreatitis ‡upper limits of normal, ¶peaks not resolved

mmol/l, range 0·22–0·57: n=11 measurements; normal range 0·80–2·20), low density lipoprotein cholesterol (mean 0·38 mmol/l, range 0·03–1·76; n=8 measurements; normal range 1·30–4·50), and total cholesterol (Table 1) were usually below the normal range as is characteristic of treated type V hyperlipoproteinaemia.[1] Lipoprotein electrophoretograms usually showed a type V pattern although occasional type IV patterns were noted.

Table 2 summarises his current diet. He remained well after his episode of pancreatitis apart from two brief recurrences of eruptive xanthomata on recent holidays. Serum lipoprotein concentrations were not measured during these episodes, but an increase in refined carbohydrate intake preceded each one. Growth has been normal and soft tissue swelling, as described by Deckelbaum *et al*, has not been noted.[4]

The boy is the youngest of three children; his parents, who are first cousins, and the siblings had normal serum lipid concentrations. Two paternal great uncles had hyperlipidaemia discovered late in adult life but further details of their diagnoses are not known.

Plasma post-heparin lipoprotein lipase activity at the age of 5 was normal, free fatty acid release from a synthetic triolein emulsion in low salt medium being 7·14 µmol/ml/hour and in high salt medium 11·76 µmol/ml/hour compared with adult control values of 6·77 and 8·27, respectively: plasma was collected 10 minutes after intravenous injection of heparin 10 U/kg.[7] Serum apolipoprotein C–II, C–III1, and C–III2 concentrations determined by polyacrylamide gel electrophoresis of very low density lipoprotein apolipoproteins in 8 M urea were

Table 2 *Diet* g/kg/24 hours (% total MJ intake) (figures in parentheses are numbers per cent)*

| | Age (years) | | | | | | |
|---|---|---|---|---|---|---|---|
| | *0·2* | *0·5* | *1* | *2* | *2·7* | *4* | *5* |
| Carbohydrate | | | | | | | |
| Total | 10 (38) | [illegible]7·4 (64) | 17·5 (64) | 12 (50) | NR | 13·3 (69) | 13·7 (70) |
| Refined | NR | [illegible]1·1 (44) | 7·9 (29) | 4·8 (20) | | 0 | 0 |
| Unrefined | NR | [illegible]5·2 (19) | 9·6 (35) | 7·2 (30) | | 13·3 (69) | 13·7 (70) |
| Fat | | | | | | | |
| Total | 6 (51) | 2·8 (23) | 2·2 (18) | 3 (28) | NR | 1·1 (13) | 1·5 (17) |
| MCT | 0 | 1·6 (13) | 0 | 0 | 0 | 0 | 0·4 (4) |
| LCT | 6 (51) | 1·2 (10) | 2·2 (18) | 3 (28) | | 1·1 (13) | 1·1 (14) |
| Polyunsaturated | 0·6 (5) | 0·6 (5) | 1·2 (10) | 0·4 (4) | | NR | 0·2 (2) |
| Total calorie intake (MJ/kg/24 hours) | | | | | | | |
| | 25 | [illegible]6 | 26 | 23 | NR | 18 | 19 |
| Clinical course | | | | | | | |
| Eruptive xanthomata | Yes | | | Yes | | | Yes |
| Pancreatitis | | | | | Yes | | |

*Calculated from three day diet diary except at 0·2 (established from recall diet), NR=not recorded normal, as were serum immunoglobulin and uric acid concentrations, serum liver function tests, and glucose tolerance test showed no abnormalities. Plasma vitamin A and E, and serum essential fatty acid concentrations have been measured yearly and have remained normal

## Discussion

The patient's clinical features are typical of both types I and V hyperlipoproteinaemia. The plasma lipid profile at 2 months of age strongly suggested the diagnosis of type V hyperlipoproteinaemia but did not exclude type I, which is a disorder seen more commonly in neonates. Familial apolipoprotein C–II deficiency is recessively inherited and may result in clinical and lipid profiles similar to those of type V hyperlipoproteinaemia. Normal PHLPL activity and apolipoprotein gel electrophoresis excluded these alternative diagnoses.[1]

Familial type V hyperlipoproteinaemia is probably an expression of several different genotypes.[2] Autosomal dominant inheritance had been well defined in some pedigrees but in other familial cases the inheritance pattern is not clear.[1 5] Greenberg *et al*[6] described a patient who was the child of a marriage of first cousins; the parents phenotypes were unfortunately not documented. Kwiterovich *et al*[2] suggested autosomal recessive inheritance with variable expression of heterozygosity as a possible explanation for some pedigrees. No obligate heterozygotes had manifest type V hyperlipoproteinaemia in the pedigree described here; neonatal onset accompanied by negative but consanguineous family history suggests an autosomal recessive inheritance pattern.

The pathogenesis of type V hyperlipoproteinaemia has not been adequately explained, although a defect in clearance of very low density lipoprotein cholesterol has been proposed as the primary abnormality.[1] Because of early onset and presumed autosomal recessive inheritance, this boy's primary defect probably differs from those of reported cases of type V hyperlipoproteinaemia and suggests aetiological heterogeneity of the disorder.[1]

For treatment of type V hyperlipoproteinaemia moderate dietary restriction (335 MJ in 24 hours for adults), restriction of regular fat (25–30% of MJ), moderate restriction of total carbohydrate (40–50% of MJ), and medium chain triglyceride supplements are recommended [1–2] Symptoms in this case dictated more severe dietary fat restriction. The recurrence of symptoms after an increase in refined carbohydrate intake without change in fat intake suggested the need for specific restriction of this form of carbohydrate. Treatment at the time of writing is therefore based on a diet that limits long chain triglycerides to about 1·5 g/kg in 24 hours and eliminates refined carbohydrate without restricting total calories. Medium chain triglyceride oil is used for cooking as a caloric supplement, but has not affected the plasma lipid profile.

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# Light transmission of phototherapy eyeshields

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SUMMARY Twelve types of phototherapy eyeshields showed peak light transmission of < 0·1%, and none transmitted > 0·04% light in the 460 nm spectral region. Commercial eyeshields offered no advantage over locally made ones. The choice of shield may be less important than how it is secured over the infant's eyes.

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Recently there has been concern that bright ambient light may be an important factor in the pathogenesis of retinopathy of prematurity,[1] yet small preterm jaundiced infants may be exposed to high levels of light during phototherapy. As a direct consequence of studies in animals that showed the damaging effects of phototherapy light on the neonatal retina,[2] human neonates receiving phototherapy now have their eyes covered routinely with eyeshields. Eyeshields are usually made according to local specifications, although commercial types are available. The effectiveness of most of these eyeshields in reducing the intensity of light, however, is unknown.

This study aimed to determine the light transmission characteristics of various commercial and locally constructed eyeshields commonly used by neonatal units in the United Kingdom.

## Methods

Of 20 neonatal units contacted, 15 provided samples of phototherapy eyeshields; 12 types were in common use. These included two commercial eyeshields manufactured specifically for use during phototherapy (Posey 4645, J T Posey Co, and Bili-Mask, Olympic Medical), a commercially manufactured orthoptic eyepatch (Opticlude, 3M); and

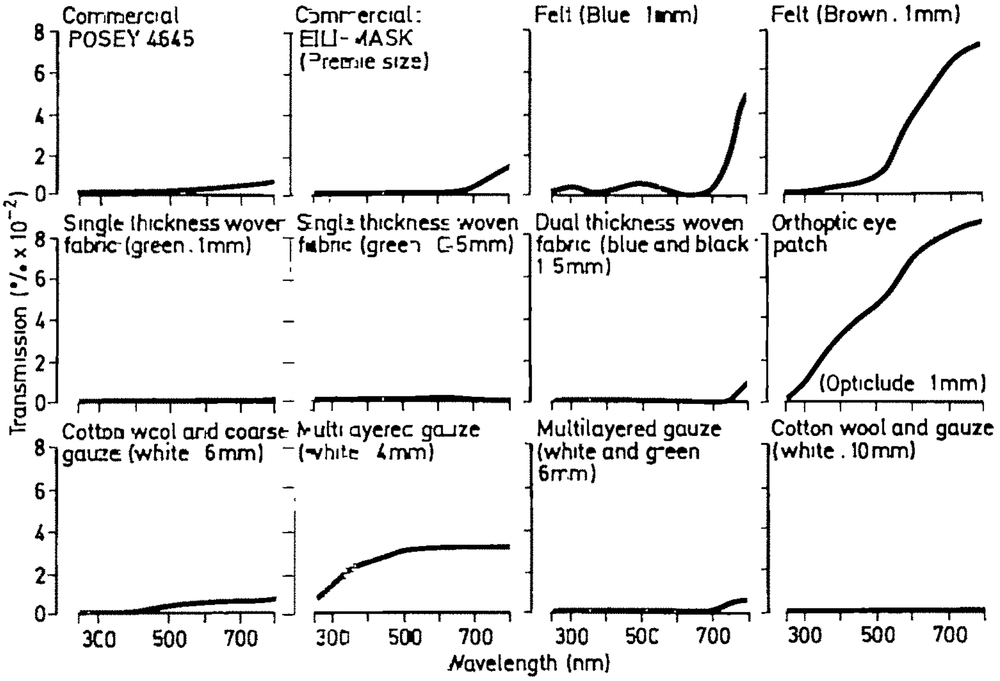

Figure *Light transmission characteristics of 12 phototherapy eyeshields. Thickness of locally made eyeshields given in mm.*

nine shields that were made of thin woven fabric (single or double layers), coloured felt, cotton wool, or gauze (single or multilayer). Light transmission was measured with a Perkin-Elmer 330 spectrophotometer (sensitivity 0·002%) in the wavelength range 250–800 nm (wavelength accuracy 0·2 nm). This wavelength range contains the spectral absorption peak of bilirubin, which is at 460 nm, and also the spectral region in which the energy from a phototherapy light source is maximal.[3]

## Results

The Figure shows the transmission measurements obtained for the 12 eyeshields. The most striking result was the extremely low level of light transmission through any of the patches. Two of the commercial patches (Posey 4645 and Bilimask) showed greatest transmission at the wavelength of 800 nm of less than 0·02%. These low values of transmission were in several cases equalled or improved on by the locally made eyeshields, especially if the patches were made of either fabric, multilayered coloured gauze, or double layered cotton wool and gauze. Even the poorest eyeshield (Opticlude, Orthoptic Eye Patch) had a peak transmission of less than 0·1%. In the critical spectral region of 460 nm none of the samples exceeded a transmission value of 0·04%.

## Discussion

Our results show that the amount of light transmitted through some commonly used phototherapy eyeshields is low and probably unimportant as a cause of retinal damage. Other studies have reported light transmission values of up to 52·5% for locally adapted eyeshields, as opposed to 1·5% transmission for a commercially available mask [4] Porat *et al* have also recorded light transmission levels of some 46% behind one layer of stockinette material illuminated by a phototherapy source. Both these studies, however, used standard photographic light meters, which are not specifically designed for carrying out light transmission measurements. Our measurements cast doubt on these studies, which indicate high levels of light transmission through noncommercial phototherapy eyeshields. It is important that measurements are made in carefully designed systems with instruments of the appropriate sensitivity Photographic light meters would be unable to measure light transmission accurately at the levels we have reported here.

Our measurements also show that commercial eyeshields offer no advantage over many locally made patches. The choice of phototherapy eyeshields may be less important than the need to ensure that the shield is effectively secured and maintained throughout the phototherapy period Both the study by Bhupathy *et al* on the short term retinal changes in neonates treated with phototherapy and that of Dobson *et al* on the long term effects on visual function failed to show any obvious changes in the retinal function of neonates whose eyes were shielded throughout phototherapy.[6 7] In contrast, Abramov *et al* tested forty five 7 year old children who had had phototherapy in the neonatal period and found major defects of cone mediated visual function in those whose eyes had not been shielded during phototherapy.[8]

We thank the nursing officers of the neonatal units who provided samples of their phototherapy eyeshields Mr Alistair Fielder provided helpful comments on our initial draft MJ Moseley is supported by the Wellcome Trust

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## *Current topic*

# Polygraphic studies

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Polygraphic recordings, simultaneous recordings of different physiological signals, have been used by physiologists for over 80 years, but their use in clinical medicine is more recent. This is partly due to the development of smaller, mobile, sophisticated recording equipment that is easy to use and supplies a great deal of information The machines are, however, costly, time consuming, and produce more data on physiological variables than it is possible to analyse I shall, therefore, review some of the clinical applications of polygraphic recordings and the problems likely to be encountered when they are used.

A polygraphic study is the simultaneous recording of two or more physiological variables over a period of time. These may be long (12–24 hours) if a changing pattern is being analysed during different activities, or sleep, or they may be short when a single event is being studied—for example, prolonged apnoea or bradycardia, or both, and their association with gastroesophageal reflux. All recordings are put on paper, magnetic tape, or both depending on the type of analysis used

## Methods

Ideally, the study should be performed in an environment controlled for light, temperature, and sound that is free from electrical interference Often, however, this is not possible and the recording has to be done in a busy ward.

**Measurements of respiratory function.** Respiration is usually recorded indirectly by impedance (intensive care monitors), abdominal and thoracic movement (strain gauges), or inductance plethysmography (Respitrace) These methods have limitations in that movement of the body interferes with the quality of the signal and obstructive apnoea cannot be diagnosed as it requires simultaneous measurement of air flow through the nares. This can be achieved by measuring either the temperature difference (thermistor) or $CO_2$ difference (capnograph) between the inspired and expired gas.

Central apnoea (loss of respiratory drive) is defined as no air flow for 10 seconds or longer, with no associated ventilatory movements of the chest or abdomen. Obstructive apnoea occurs when there is no air flow but continued chest and abdominal ventilatory movements. Quantitative measurements of gas flow are usually made with a pneumotachometer, which is attached to a mask applied firmly to the face or nares. The tactile stimulation of an infant's face, however, alters respiratory patterns and therefore limits the use of the mask[1] A quantitative measurement can be made without a face mask using the barometric plethysmograph.[2] This is accurate and reliable but is complex and expensive to install, and its use is limited to a few research centres

**Measurements of oxygen concentration.** Arterial oxygen concentrations are usually measured as saturation by a pulse oximeter. The advantages over transcutaneous oxygen tension measurements are the rapid response time, ease of calibration, and ease of use; the electrode has no membrane to damage and can remain attached to the limb or ear for long periods

**Measurements of cardiovascular function.** The electrocardiogram (ECG) is recorded with the standard four lead system. The two chest leads may also be used for the impedance respiratory monitor.

**Measurements of central nervous system functions.** The electroencephalogram (EEG) is used to define sleep states using a three electrode or multielectrode system following the 10/20 configuration. If there is a possibility of seizures, the continuous EEG is sometimes combined with video monitoring.

**Measurements of musculoskeletal function.** In many sleep study laboratories surface electromyograms (EMG) recorded from extra-ocular muscles are used to define rapid eye movement sleep. Additional information about the respiratory system is sometimes obtained using surface EMGs from intercostal muscles to measure chest wall distortion, and from the diaphragm to estimate muscle fatigue.

**Oesophageal pH.** An indwelling oesophageal electrode giving a continuous reading is used to detect acid regurgitation into the lower oesophagus, which is an index of gastroesophageal reflux.

**Measurement of sleep states.** In normal infants and children, patterns of breathing and heart rate vary in different sleep states In quiet sleep (non-rapid eye movement) the breathing pattern is regular with little variability, while in active sleep (rapid eye movement) variability is wide and apnoea common.[3] The definitions of states are, therefore, important in the interpretation of respiratory and cardiac patterns. To define sleep states most laboratories use a combination of behavioural signs—for example, body movement, facial and eye movements, vocal sounds, and EEG readings.[4 5] Unfortunately no one system is accepted by everybody, making comparison of results among laboratories difficult.

## Data analysis

Analysis of a 12 hour recording is often difficult as there may be over 400 pages of data. Sometimes analysis consists of flipping through the pages and picking out any abnormal sections for further analysis. Computer analysis requires a magnetic tape record and its success depends on the quality of the signal, the questions asked, and the program used Electrocardiographic signals are best interpreted by recording heart beat intervals in milliseconds and measuring median beat intervals and their interquantile range for long term variability and differences in successive beat intervals for short term variability Bradycardias are easily isolated and can be edited separately Respiratory signals are more difficult to analyse as they are particularly sensitive to body movement, and baseline shift is common. Analysis usually entails measuring breath to breath intervals (breathing rate) and their variability. Data may be obtained in different sleep states on the occurrence (%) of bradycardia, central apnoea, and its duration This information is important for defining normality at different ages when defects in maturation are postulated.

Analysis of life threatening events is still best done by hand. In long recordings this is only possible using magnetic tape records, from which events may be abstracted and written out separately Because tapes may be edited, and replayed over and over again for reanalysis as new theories emerge, they are invaluable in polygraphic studies. When two physiological variables are compared the response time of the recording instruments must be known as, for example, some transcutaneous oxygen instruments have a delay of 12 seconds or more.

The person analysing the record must be able to say what the readings mean, and whether they lie within the normal range, which may be difficult

## Clinical applications

**Screening for sudden infant death syndrome.** Despite a lot of research, sudden infant death syndrome cannot be predicted or excluded by polygraphic studies.[6 7] Suspected risk factors such as apnoea and periodic breathing are seen in normal subjects,[8 9] as are extrasystoles, bradycardias, sinus pauses, and nodal rhythms.[10 11] It is this new information about the wide range of normality that polygraphic studies have contributed to clinical medicine As one clinician quoted in a recent review about ambulatory ECG said 'a normal person may be defined as someone who has not been adequately investigated'[10] The wide range of normality has made the isolation of true abnormality difficult; in some patients loss of variation indicates abnormality, for example infants with severe congenital malformations of the lung[12] In others, the variation may occur too frequently, inappropriately, or be prolonged It is in this group that there is the greatest difficulty in defining true abnormality, and in the past the wrong diagnosis may have been made if age matched controls were not studied as well For example, in some healthy full term infants sustained episodes of periodic breathing are rare in the first week, become common between two and four months, and decrease thereafter[8]

**The investigation of life threatening events.** Many studies have shown that polygraphic recordings may help in the diagnosis and management of recurrent life threatening events[13] Ideally the event occurs while the recordings are being made. In practice this is unlikely to happen because of the random occurrence of the events, and the vagaries of electronic equipment Events usually affect the respiratory, cardiac, or central nervous systems. The recording at the time of an event should confirm whether an event has occurred and, whether one or more system was affected, it should also indicate which system was most seriously affected and the possible factors causing the event

Of all respiratory events, prolonged central apnoea during quiet sleep is the easiest to diagnose, as body movement is absent and a good quality recording can be made. Obstructive apnoea, either in isolation or combined with central apnoea, is more difficult because it is usually associated with body movement, which causes interference to the respiratory signal, in addition, two simultaneous recordings are needed. Obstructive apnoea is often associated with obvious bradycardia, continued ventilatory effort,[14] and a drop in oxygen saturation The obstruction may be due to an abnormality of the oropharynx, or it may be secondary to gastroesophageal reflux. Abnormality of the oropharynx may be easy to diagnose as in the Pierre Robin syndrome, where the cleft in the soft palate, small jaw, and posteriorly placed tongue leads to obstruction of the laryngeal inlet. Enlarged tonsils, adenoids, and uvula can also obstruct breathing, but it is only from studies of follow up data after surgery that the problem may be put into perspective.[15 16]

The assessment of the role of gastroesophageal reflux is just as difficult. Acid regurgitation will be recorded by the oesophageal pH monitor, and it can be correlated with the apnoea provided that all signals are recorded on the same record or that they share a common time base. The difficulty lies in their interpretation. Gastroesophageal reflux seems to occur with body movement when the infant is awake[17] or in active sleep,[18] a time when apnoea is common. Analysis of the timing of reflux and apnoea suggests that most episodes of prolonged apnoea are not accompanied by reflux[19] and that the events are not necessarily associated.[20] This conclusion has been challenged, and it seems likely that a few infants present with obstructive apnoea caused by gastroesophageal reflux when awake.[21]

If the life threatening events are caused by recurrent abnormalities in cardiac rhythm these should be obvious on the ECG tracing as it is not grossly affected by body movement. Accurate diagnosis depends on an ECG tracing before, during, and after the event, so that all the components of the ECG may be analysed If the period of study is prolonged a magnetic tape record is necessary for this type of analysis.

**Polygraphic studies and epilepsy.** Epilepsy alone can be difficult to diagnose, as loss of consciousness may be caused by a cardiac arrhythmia rather than a cerebral lesion.[22] Conversely, partial seizures in newborn babies may be accompanied by apnoea and bradycardia.[23]

Considerable improvements have been made in the accuracy of diagnosis by simultaneous EEG recording and video monitoring.[24] The advantage of the technique is that the event can be repeatedly reviewed, and carefully defined, both in terms of the child's behaviour and serial EEG recordings. This objective technique has helped in the diagnosis of different types of epilepsy, their localisation, quantification, and response to drug treatment.[25]

The technique may also be of value in diagnosing neonatal seizures. This diagnosis is still largely based on clinical observations without reference to EEG tracings [26] In 1983 Eyre *et al*[27] reported a technique for the rapid analysis of EEG tracings to diagnose neonatal seizures. Unfortunately tonic seizures are not always accompanied by EEG abnormalities, in a study of 400 tonic seizures in 120 babies, 102 episodes had no accompanying seizure activity on EEG.[28] The concept that so called tonic seizures in newborn babies are due to epileptic discharges in the brain needs to be re-examined. The opposite may also be true, in that some EEG seizures are not accompanied by abnormal behaviour; one series reported a figure of 79% of 393 electrographic seizures analysed.[29] As this technique becomes more available, our clinical definition of epilepsy will become more sensitive and our treatment more appropriate. In the newborn period this is particularly important because of the strong association between seizures and permanent handicap.[30]

## Summary

Polygraphic recordings have provided new information about the wide ranges of normality in various diseases and the process of maturation from birth to childhood. New techniques will help to document clinical events accurately, improve diagnosis, and evaluate treatment.

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*Archives of Disease in Childhood,* 1987, **62,** 976–979

# Correspondence

## Ventilator settings for newborn infants

Sir,

For those not intimately involved in ventilating critically ill low birthweight babies, the excellent article by Ramsden *et al*[1] and the commentaries by South and Morley, and by Milner, could leave them feeling bemused.

In terms of getting babies with severe surfactant deficient respiratory distress syndrome through the first four to five days, it does not matter how you set the ventilator because there are many ways to oxygenate and blow off $CO_2$ in such patients. The best proof of this statement is the fact that it is now extremely rare for a baby to die from respiratory distress syndrome alone.

Babies with severe respiratory distress syndrome who die in the first few days do so from infection, some form of air leak, or from periventricular haemorrhage. I submit that there is little evidence that different ventilator settings have much impact on the morbidity or mortality from these complications. Paralysing babies may occasionally help; and at the mild end of the spectrum (unsatisfactory though the studies are) it is possible that faster rates, around 60 (but not 100–120), are associated with a lower incidence of air leak syndrome. If, however, a lot of babies in your unit are dying from respiratory distress syndrome, you should not be worrying about what rate to set your ventilator but whether you are in the right specialty!

The crucial question is the incidence of chronic lung disease. As the paper by Ramsden *et al* points out, the 'slow' rate techniques were introduced at University College Hospital in the late 1960s when they had a very high incidence of severe bronchopulmonary dysplasia. Despite the deficiencies in their data, which they freely acknowledge, their studies are the only ones that show that varying the ventilator settings can have any effect on the incidence of chronic lung disease, and that the slower rates with a high mean airway pressure are safest from this point of view.

As severe chronic lung disease is now one of the major clinical problems we are facing associated with the increased survival of infants of less than 1000 g birth weight, no study of neonatal ventilation is worth the paper it is published on unless it addresses this problem. I would submit that the protagonists of fast ventilator rates are merely advocating an experimental procedure until they can show conclusively that their methods of ventilating are not associated with the high incidence of chronic lung disease that was observed with similar techniques 20 years ago.

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Sir,

I read with interest the paper by Ramsden *et al* on ventilator settings for newborn infants.[1] The majority of babies who require ventilation suffer from respiratory distress associated with prematurity. When studies are carried out which include only such infants, meaningful conclusions from the results can be drawn. Recently, we have successfully answered the question of which ventilator rate is most beneficial in such a homogeneous group of infants—those with pneumonia, apnoea, and pulmonary hypoplasia, we excluded those with meconium aspiration.[2] We found that fast rates (greater than 100/minute) were associated with a significant increase in both oxygenation and carbon dioxide removal when compared to slower rates. The explanation for this was (as we subsequently showed[3]) that at such rates infants breathe in synchrony with their ventilator. We found that the spontaneous respiratory rate of ventilated infants during the first 24 hours of life was inversely proportional to their gestational age. Thus the faster ventilator frequency more closely mimicked the infant's spontaneous respiratory rate and induced synchronous respiration.

Increasing the ventilator rate can also, by inducing synchrony, reduce active expiration and hence the necessity for paralysis. Numerous although possibly not well designed studies have suggested that fast rates reduce the incidence of pneumothorax. When this evidence is considered with the improvement in gas exchange at increased ventilator frequencies,[2] it must suggest that fast rates are appropriate for preterm infants with respiratory distress. I agree, however, that fast rates are not the panacea for all ventilated infants. Relatively 'mature' infants with severe respiratory distress syndrome constitute a separate group and I would—and do—ventilate such infants at slower rates. Optimal types of artificial ventilation for other diagnoses such as pneumonia, pulmonary hypoplasia, and meconium aspiration remain untested.

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# Investigation of children with enuresis and urinary tract infections

Sir,

I wonder if other paediatricians will join me in deploring the invasive investigations perpetrated on children with urinary tract infections.

Two recent papers in the *Archives*, from Leeds[1] and Melbourne,[2] report that after a urinary tract infection micturating cystourethrograms were performed on almost all, and intravenous urograms on many, of the children, during studies on daytime enuresis and urinary nitrite, respectively.

It is over 10 years since we showed in Derby that it is possible to exclude severe reflux (the main abnormality found on a micturating cystourethrogram) in 90% of cases by examining the intravenous urogram carefully,[3] and last year we showed that ultrasonography is almost as reliable as intravenous urography in detecting important renal tract abnormalities.[4] Micturating cystography is a potentially dangerous,[5] and extremely unpleasant investigation (ask the children) and an intravenous urogram little better. In most children they can reliably be replaced by ultrasonography as the first investigation.

I believe that paediatricians have an obligation to their patients to protect them from these painful and usually unnecessary tests.

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Professor Meadow comments:

The children included in the Leeds study had been investigated in different units at various times in the past. I am sure that if their investigation had been more recent ultrasonography of the renal tract combined with straight abdominal *x*-ray would have been the prime investigation for many of the children.

I share some but not all of Dr Moncrieff's enthusiasm for ultrasonography; it does have its limitations. Ultrasound is much better for visualisation of the upper urinary tract than the lower, and inadequate for detecting urethral lesions. It depends on a committed and skilled operator. Moreover, because there are not yet agreed standard procedures for ultrasonography, one does not have comparable sets of hard pictures for others to study and discuss at *x*-ray meetings and joint clinics. Until such standard sets of pictures are available and clinicians have learnt to interpret them, ultrasonography is likely to be associated with more misinterpretations than a standard intravenous urogram.

Dr Powell comments:

Dr Moncrieff's remarks are largely irrelevant to the main purpose of our report which concerned the effects of urinary frequency on the nitrite dip strip test. His comments do, however, illustrate the divergence of opinion on the need for, and best methods of, investigation after diagnosis of urinary tract infection. With the accumulating evidence that urinary reflux only rarely leads to new renal damage in older children we would now agree with Dr Moncrieff that voiding cystography is usually unnecessary in children over 5 years old and that good quality ultrasound, if available, can replace the intravenous urogram. The intravenous urogram is generally performed well, even in small centres, which frequently have difficulty providing good quality ultrasound examinations. Thus the choice of investigation depends on the quality of the organ imaging service locally available. At this hospital, we now recommend an ultrasound and cystogram on all patients under 5 years old with urinary tract infections and an ultrasound alone on older children.

# Diagnosis and management of urinary tract infection

Sir,

I read with interest the recent article by Professor White[1] and an earlier one by Dr Haycock,[2] about childhood urinary tract infection.

There is little disagreement about the limited need for a routine micturating cystourethrogram in older children with recurrent urinary tract infection. The procedure may introduce infection, is painful, and occasionally dangerous.[3] I would therefore like to emphasise the importance of pre- and post micturition ultrasound examination in such cases.

In the last eight months we have seen four girls, aged 7 to 12 years, referred because of recurrent urinary tract infection in spite of continuous antibiotic prophylaxis. Ultrasound examinations and intravenous pyelograms were normal. Repeat ultrasound examinations, including pre- and post micturition examination showed incomplete emptying of the bladder that was subsequently confirmed by micturating cystourethrography. Cystoscopy showed minor degrees of outlet obstruction in two cases, severe trigonitis in one, and a poorly functioning atonic bladder in the remaining case.

In view of its widespread availability and non-invasive nature, children (particularly over 5 years old) with recurrent urinary tract infections should have routine pre- and post micturition ultrasound examinations. Similarly, a post micturition film after an intravenous pyelogram may be helpful.

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## Management of urinary tract infection

Sir,

In his Personal Practice paper,[1] Professor R H R White states that in the investigation of urinary tract infections by ultrasonography 'it is prudent to combine this procedure with a plain abdominal radiograph to exclude radio-opaque calculi and facilitate review of the lumbosacral spine'

His yield of opaque calculi may be increased if he requests a plain abdominal radiograph after a drink—a technique most x-ray departments already use for improving the results of an intravenous urogram

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[1] White RHR Management of urinary tract infection *Arch Dis Child* 1987,62:421–7

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## The physically handicapped school leaver

Sir,

M Ann Chamberlain contributes a generous annotation[1] based on our pamphlet 'The health and social needs of physically handicapped young adults—are they being met by the statutory services'?[2] We must, however, correct one or two inaccuracies

Chamberlain refers to the report as 'The Spastics' Society Report' It was of course written by us and is not a report from the Spastics' Society, and certainly does not represent either their policies or necessarily their views. The views are our own

In the penultimate paragraph she quotes the report as suggesting that we were proposing a sub specialist grade to treat adolescents. We were, in fact, careful not to do this. We talked about the setting up of a district based handicapped adult team and I would agree with her view that an adult specialist needs to be appointed to take on this task

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## Varioliform gastritis and campylobacter-like organisms

Sir,

We read with interest the report of a paediatric case of varioliform gastritis by Caporali *et al*,[1] supporting the idea that this endoscopic picture has an allergic aetiology We have recently reviewed our upper digestive endoscopy findings in children retrospectively looking for histologic evidence of campylobacter-like organisms Among children with histologic evidence of such infection of gastric mucosa we found a 9 year old girl who was admitted with anorexia, epigastric pain, and vomiting Endoscopy showed typical scattered umbilicated papular lesions called varioliform gastritis in the antrum and the body of the stomach. Histological examination showed poly- and mononuclear infiltration in gastric specimens (fig 1) associated with the presence of bacteria under the mucus layer (fig 2) No evidence of in vivo or in vitro food allergy was found Follow up of this patient was not possible because she moved to another country

Recently campylobacter-like organisms were shown to be associated with gastritis, and gastric and duodenal ulcers both in adults and in children [2] Even though a specific endoscopic picture has not been described, the occurrence of antral nodularity and histological gastritis has been found in children with this disease.[2 3] The

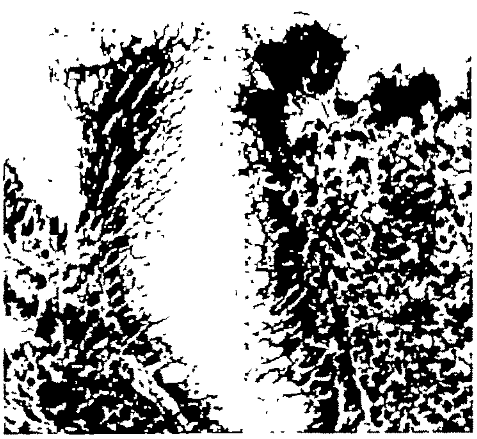

Fig 1 *Diffuse interstitial inflammation of antral mucosa with irregular cell profiles Giemsa.*

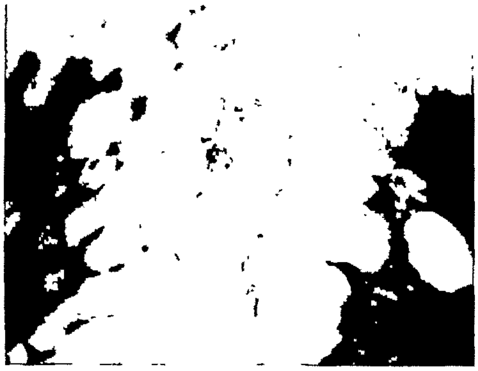

Fig 2 *At higher magnification numerous campylobacter-like organisms adhering to the luminar surface of foveolate epithelium Giemsa*

outcome of the infection in a child with dyspepsia but no ulcer varioliform gastritis might indicate that this peculiar endoscopic picture is probably not specific to a particular aetiology As histological diagnosis of campylobacter-like infection is possible also on formalin fixed specimens if the Warthin-Starry or Giemsa stains are used, we suggest that the association between it and varioliform gastritis may be easily confirmed in a large series

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## Haemorrhagic disease and vitamin K

Sir,

In their recent annotation[1] Tripp *et al* state their preference for using oral vitamin $K_1$ for routine prophylaxis against haemorrhagic disease of the newborn. They felt that convenience and acceptability to the parents were sufficient grounds for recommending a 1 mg dose to be given orally routinely unless there was evidence of the baby being at high risk of haemorrhagic disease In support of this recommendation, they state that they have not seen any case of early or late haemorrhagic disease in 25 000 babies treated in this manner

The experience in Sheffield using oral prophylaxis has been less satisfactory Routine prophylaxis was introduced three years ago following a cluster of cases of late haemorrhagic disease occurring between three and seven weeks after birth Two of the maternity units in the city use intramuscular, and the third unit uses oral prophylaxis One of the babies who received 1 mg of vitamin $K_1$ orally in the labour ward subsequently developed severe haemorrhagic disease at 7 weeks of age He was born at full term weighing 4100 g and was fully breast fed He was completely well until he developed convulsions at 7 weeks of age due to an enormous intracerebral haematoma occupying the posterior half of the left hemisphere He had severe vitamin K deficiency which was corrected rapidly with treatment He has subsequently made a good recovery He had no predisposing reason for the vitamin K deficiency, and his sweat test was negative. His mother was well throughout the pregnancy and received no drugs other than iron and vitamins

Haemorrhagic disease has always been uncommon even without routine prophylaxis The aim is to prevent an uncommon, but potentially fatal, disorder We feel that vitamin K given intramuscularly is more likely to prevent this serious condition than if it is given orally

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## Skin rashes after triple vaccine

Sir,

With regard to the article by Denning *et al*[1] on rashes after diphtheria-pertussis-tetanus (DPT) vaccine, I have seen an eczematous reaction concentrated around an aluminium granuloma following DPT, spreading to the trunk, but tapering off from the injection site There was no history of previous eczema I did not risk giving another DPT injection An article in the *Practitioner* described similar skin reactions [2]

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# Book reviews

**Pediatric Diagnosis. Interpretation of Symptoms and Signs in Different Age Periods.** Morris Green. 4th edition Pp 496: £39·50 hardback W B Saunders, 1986

Experienced paediatricians recognise that clinical diagnosis is a holistic process by which initial impressions of complaint, child, and family rapidly generate a probable explanation Conscientious medical practice demands that this preliminary diagnosis be tested by the discipline of a full history, and examination supported, if warranted, by appropriate investigation The excitement of paediatrics is that all this has to be related to the dynamics of development, and the changing spectrum of age related disorders. This book attempts to unravel and illuminate this diagnostic process. The first half is a systemic analysis of the clues provided by physical examination It is a compendium of diagnostic possibilities for almost all conceivable signs, from scalp alopecia to macrodactyly of the large toe The second half provides a problem orientated approach to regularly encountered complaints, both organic and behavioural Both sections are set out clearly with liberal subheadings, and relevant, up to date references are included in the text

The underlying concept of this book will not appeal to all readers, particularly those reared on more traditional texts encompassing diagnosis, natural history, and treatment Its potential strength lies in providing a useful approach to taxing problems, and in provoking a wider differential diagnosis when faced with apparently straightforward situations I took issue with the priority given within some of the lists of disorders; and the design of the book inevitably creates an artificial divide between presenting features, age, and the all important growth pattern of the child

Young paediatricians preparing for examinations would benefit from delving through the book, but preferably after they have consolidated their factual knowledge An aspiring candidate would have to be supremely confident to cope with the onslaught of syndromes and eponymous terms The first diagnosis encountered on page one is the Coffin-Siris syndrome, immediately followed by a list of 22 largely exotic disorders Less well prepared readers might see some subtle logic in the comment on depression and anxiety in the following paragraph! The message is that this book deserves a place on your reserve reading list, and that it should lie alongside *Nelson* or *Forfar and Arneil*

D I JOHNSTON

**Paediatric Body CT.** Alan Daneman Pp 374: £135·00 hardback. Springer-Verlag, 1987.

Computed tomography (CT) has not made quite the same inroads into imaging in paediatrics as it has in adult medicine The main reasons for this are that the resolution of ultrasound scans is better in small objects than in large objects whereas the resolution of computed tomography scans is virtually fixed, and secondly, the absence of intra-abdominal fat from children enhances the quality of ultrasound scans whereas it detracts from the clarity of CT scans. Add to these factors the different range of pathology encountered in children and it is clear that the role of CT in paediatrics cannot be extrapolated from adult practice, but needs special consideration.

From his experience at the Hospital for Sick Children in Toronto, Dr Daneman has produced an excellent review of the techniques, applications, and results of CT of the body in children After a short general introduction the major anatomical areas are considered in consecutive chapters. Additional chapters discuss techniques for thoracic and abdominal examinations and for scans of the neck and extremities. An account of the CT features of the common pathologies in each anatomical area is prefaced in most chapters by a summary of the relevant anatomy and normal CT appearances

The experience of the author and his colleagues is clearly very extensive, and it is difficult to pick out any major gaps in the range of pathology that is discussed and illustrated. There is a pleasing uniformity of style and an absence of overlap or contradiction between different chapters, qualities which clearly relate to the single author format. The illustrations (over 300 in all) are generally of good quality, although rather oddly, a few have been printed in black and white instead of the usual white on black. Throughout the text the author places the use of CT in context with other imaging procedures, so that where ultrasound or scintigraphy is the preferred method (such as in the assessment of transplanted kidneys), he does not hesitate to say so. In summary, this is an excellent account of the use of CT in children and is thoroughly recommended.

P J ROBINSON

**Children with Cancer. A Comprehensive Reference Guide for Parents.** Jeanne Munn Bracken Pp 407: £20 hardback Oxford University Press, 1986

As the title suggests this is a very detailed book written by the mother of a child with a solid tumour It covers both the medical and psychological aspects of childhood malignancy and contains personal tips on how to help your child through diagnosis and treatment and how to cope as a family with the emotional problems One chapter is devoted to the adolescent cancer patient. Although the child is a long term survivor, the author deals realistically throughout the book with the possibility of treatment being unsuccessful She gives some practical advice on the dying child and what to do if another child attending the clinic dies.

An appendix simply outlines medical tests and a glossary explains commonly used medical terms Not surprisingly, as the author is a reference librarian, there is a good bibliography at the end of each chapter.

The book is written by an American and its overall slant is biased towards American medicine and the problems thereof, some of which—for example, the financial ones—fortunately, are not really applicable in the United Kingdom. Nevertheless, it would be a helpful guide for parents who require further written information or for any lay person seeking a comprehensive book on childhood malignancy

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**Indications** Epilepsy (generalised tonic-clonic and partial seizures).
**Dosage in epilepsy** Use a gradually increasing dosage scheme, adjusting to patient's needs. Adults: 100-200mg once or twice daily, increasing slowly up to 800-1,200mg daily; in some cases 1,600mg daily may be necessary. Children: up to 1 year old, 100-200mg daily; aged 1-5 years, 200-400mg daily; aged 5-10 years, 400-600mg daily; aged 10-15 years, 600-1,000mg daily. It may be helpful to monitor plasma drug levels: optimum therapeutic range is 3-10$\mu$g/ml (13-42$\mu$mols/l).
**Side-effects** Dizziness and diplopia (usually dose-dependent), less frequently dry mouth, nausea and vomiting. Generalised erythematous rash, disappearing on cessation of therapy. Isolated reports of oedema, hyponatraemia, exfoliative dermatitis, leucopenia, thrombocytopenia, agranulocytosis, aplastic anaemia, cholestatic jaundice and acute renal failure. Blood count should be checked in early stages of treatment.
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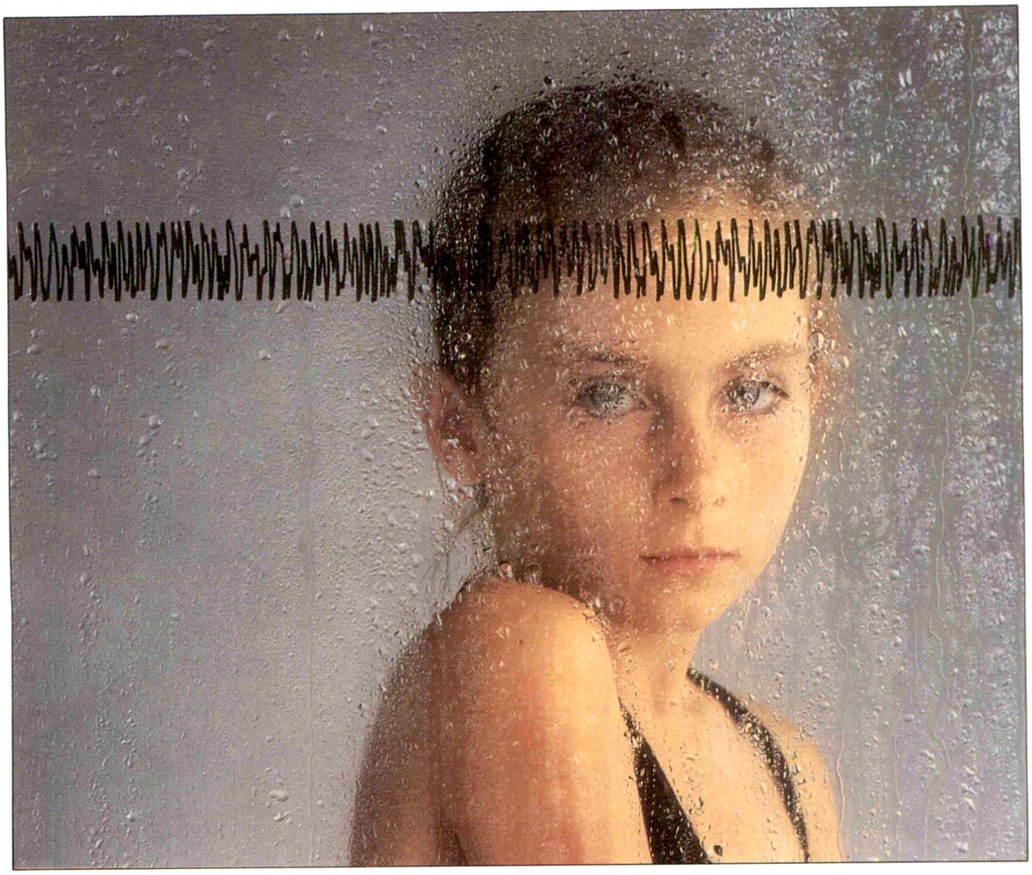

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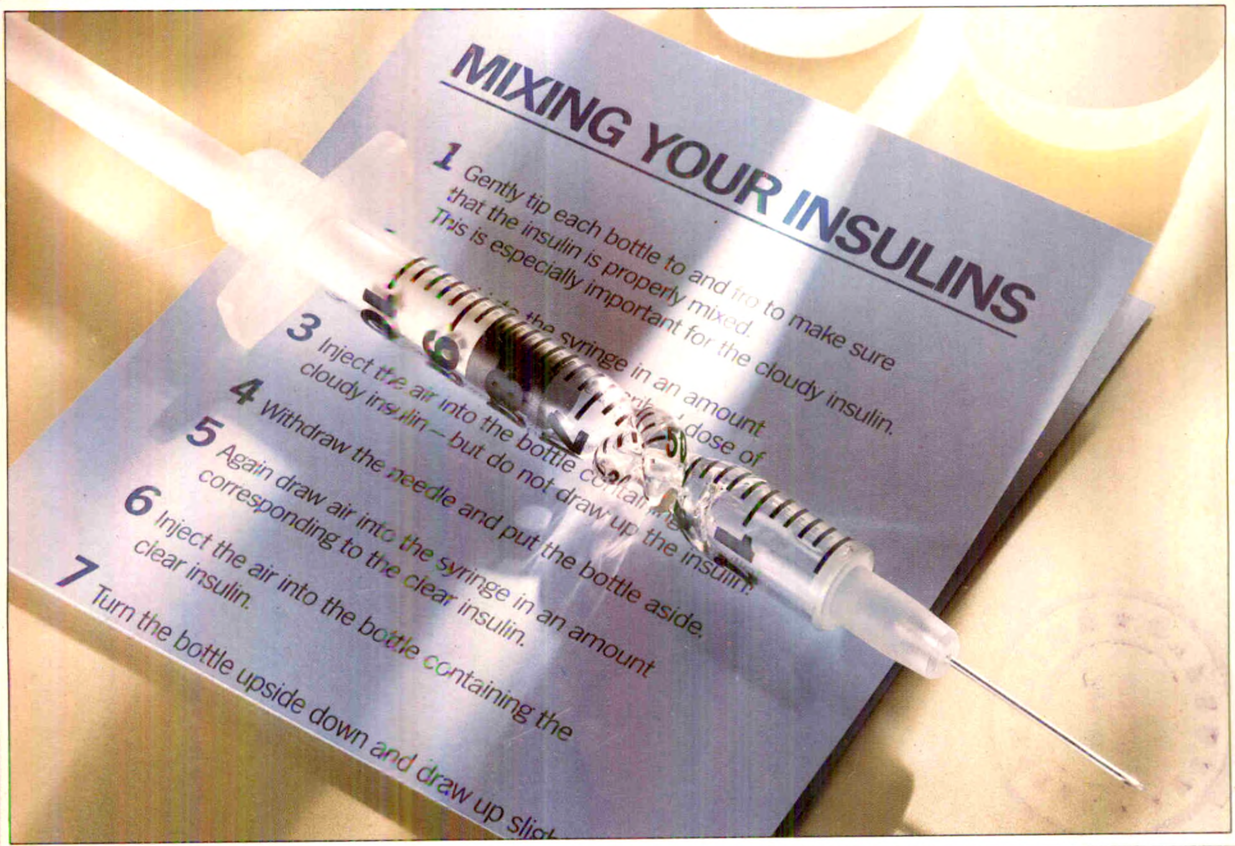

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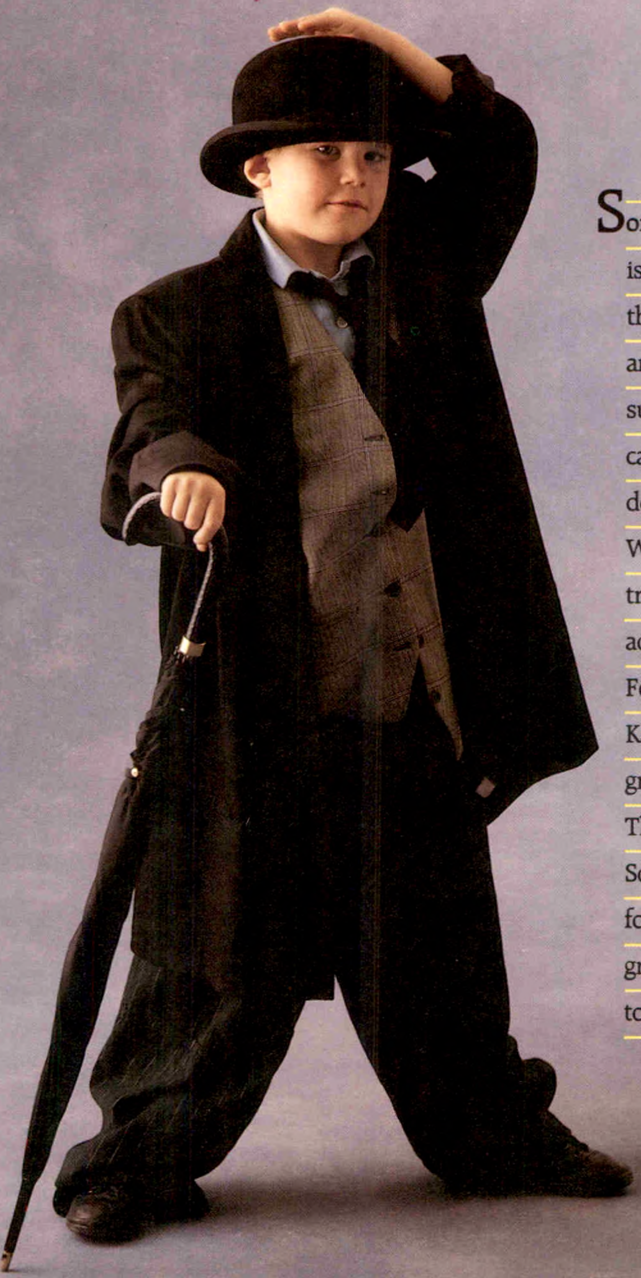

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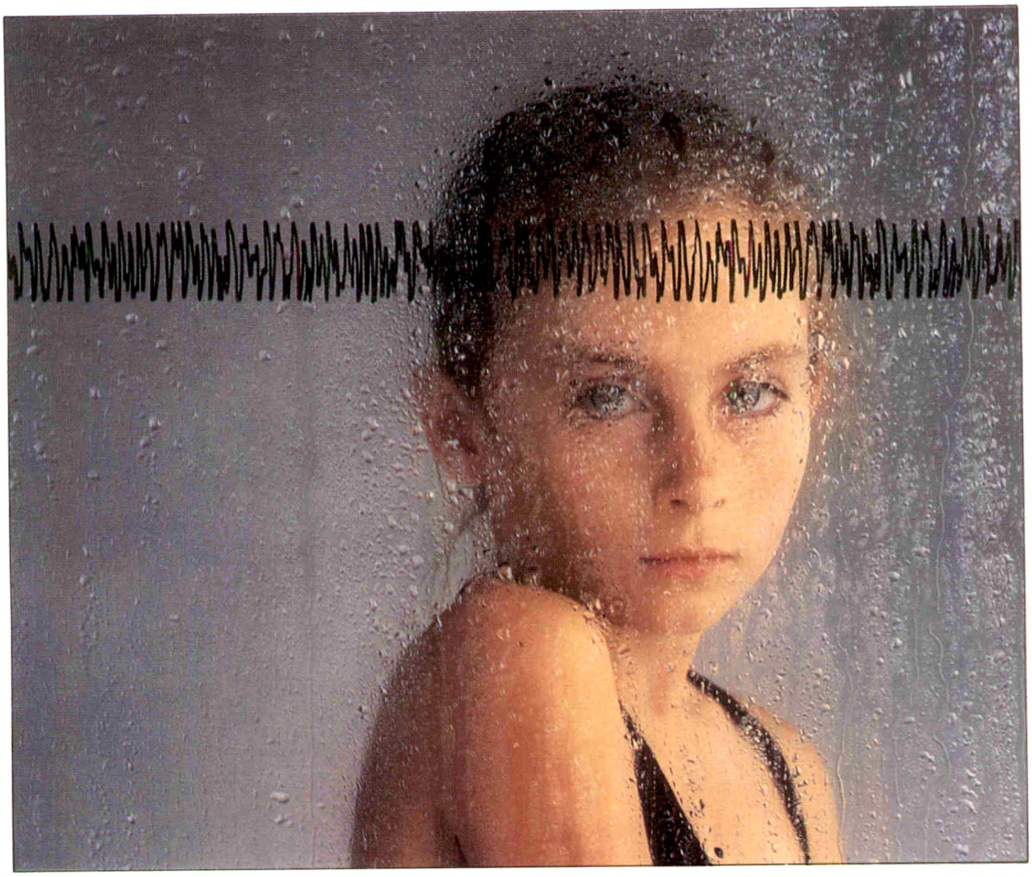

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# *helps to maintain the normality of life*

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## *Editorial*

# Associate editors

Four years ago the number of papers submitted to the *'Archives'* began to rise steeply and it became clear that a new editorial structure was needed. When the journal was founded two Joint Editors were appointed and this arrangement continued. During the war years, while one of the Editors was often away on active service, an Assistant Editor was appointed. We considered the appointment of a full-time Editor but thought that the lack of constant contact with clinical and research problems would be a disadvantage. As the blossoming of paediatric specialty groups produced papers which needed an increasing breadth of technical knowledge for critical evaluation we adopted a system of associate editors who, by their specific experience, could assist the Editors in the assessment of papers.

Two years ago we appointed Dr Malcolm Chiswick as Associate Editor in perinatal medicine and this pilot run showed that the system worked. When Dr Chiswick became Joint Editor three associate editors were appointed: Professor David Milner, Dr Richard Robinson, and Dr Brian Wharton.

*Professor Milner* has been Head of the Department of Paediatrics at Sheffield for 12 years. He is Chairman of one of the largest grants committees of the Medical Research Council and is Treasurer of the Neonatal Society. He has a special clinical and research interest in diabetes mellitus and growth disorders and his broadly based laboratory studies include the role of peptide growth factors.

*Dr Robinson* was appointed Consultant Paediatric Neurologist to Guy's Hospital, London, in 1979. He is Chairman of the British Paediatric Neurology Association. He has continued his early research in cerebral blood flow and has explored the effects of insults to the brain, including encephalitis, head injury, and cardiac arrest.

*Dr Wharton* has been Consultant Paediatrician and Senior Lecturer in Birmingham since 1973. He is Convenor of the Nutrition Committee of the British Paediatric Association and Chairman of the Committee on Nutrition of the Low Birth Baby instituted by the European Society of Paediatric Gastroenterology and Nutrition. After a grounding in kwashiorkor his research progressed through gastrointestinal disorders; maternal, fetal, and neonatal nutrition; to the deficiencies of the older child.

All papers submitted for publication are seen and discussed by both Editors who make the final decision on publication in the light of reports from referees. This practice will continue. The associate editors will receive papers in their own fields, obtain referees' reports, and make recommendations to the Editors who will take the final decision. Where a paper has been received by an Associate Editor he will correspond with the author, convey the decision, and where appropriate, negotiate improvements in the paper in the light of his own judgment and the referee's report. The final accepted version of the manuscript is managed by the Technical Editor who will make adjustments to improve clarity and presentation and insert the instructions for the printers.

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## *Annotations*

# Screening for squint and poor vision

Screening, the economical method of detecting disease before symptoms occur, does not carry with it the stimulating cachet of technological medicine, when one considers that a substantial proportion of visual defects in children are preventable, however, the importance of screening of vision begins to take on a new light. Preventable visual defects in childhood include those caused by congenital cataracts, congenital glaucoma, bilateral high ametropia, retinoblastoma, and possibly, retrolental fibroplasia. Congenital cataract is by far the largest preventable cause of bilateral visual defects. In addition to this, a relatively small number (about 4% of the population), have amblyopia secondary to refractive error or squint. These cases are almost invariably unilateral.

What constitutes a visual handicap? Any bilateral untreatable visual defect gives rise to visual handicap of varying degree. For screening, the real question is whether unilateral amblyopia results in a handicap sufficient to make screening economically or socially worthwhile. The risk of injury to the non-amblyopic eye is about 1·75/1000 amblyopic subjects in Finland.[1] Applied to this country, this would mean that there are about 2000 people (or 25 each year) blinded in this way. Amblyopia is often detected by parents who notice the associated squint, and only a proportion are likely to be detected before symptoms occur.

### What test are currently used?

The tester usually takes a history of the parents' observations and a family history; he will carry out an external inspection, look at the corneal reflections of a light to see if they are symmetrical, and carry out a cover test.[2] An orthoptist will carry out additional tests to detect abnormalities of binocular vision. If a doctor is doing the testing, an ophthalmoscope will be used to detect abnormalities of the refractive media: only rarely is refraction part of screening.

### When do we carry out these tests?

Every baby has a neonatal test and this is followed, with regional variations, by tests at 6 weeks, 8 months, 18–21 months, and 3 to 3½ years by the general practitioner, community paediatrician, or a health visitor, and, in a few regions, a community orthoptist will carry out screening tests at some stage. In principle, this scheme provides an adequate screening programme, but one which is often flawed for the following reasons.

The tests may be carried out at the wrong time. The 3½ year test probably detects an inadequate proportion of visual defects and detects many amblyopic children too late for optimal treatment.[3] The neonatal test is good but should be modified by paediatricians to detect errors of the refractive media.[4] A 6 week test is also timely, but external inspection alone is not likely to detect amblyopia or squint at this age when the child does not yet have good fixation. The test at 8–9 months that is currently carried out should be replaced by a test between 3 and 6 months which is a better time to treat bilateral diseases, especially congenital cataract. The 18–21 month test should probably be replaced by one at 1 year and possibly one at 2 years, followed by a preschool and biannual school test.

The present tests do not detect disease accurately and are poorly performed. The neonatal test and the tests in infancy should be modified to detect errors in the refractive media.[4] If a bright direct ophthalmoscope is held about 18 inches away from a neonate's eye, with the observer looking down the beam of light from the ophthalmoscope into the eye, a bright red reflex is normally seen in fair haired children and a dark red or greyish reflex in brown or black skinned children. Anything which prevents this reflex from being seen by the observer should be interpreted as an abnormality in the refractive media, and these children need to be referred to an ophthalmologist without delay. Every child should be examined in this way as part of the neonatal test.

The standard of testing is often poor with too many false positive and false negative results. Couldn't orthoptists put their undoubted skills to better use in training than in testing?

The tests should be modified, especially in the older age groups, to simplify the procedures. For instance, the use of a stereogram,[5] a more widespread use of the Sheridan Gardiner, or other figure matching or naming techniques, may also be helpful.

The taking of a brief family history and listening to the parents' observations would improve selection and help to develop an 'at risk' concept.

### What happens to the screened children?

If they are abnormal, especially if below 3 years of age, they are usually referred to an ophthalmologist. Older than 3 years, they are usually referred to an optician or an ophthalmic medical practitioner (a doctor who refracts and works in a medical eye centre). If the problem is non-refractive, children should be referred to an ophthalmologist. The outstanding problem is that if any changes in screening were to result in larger numbers of referrals, an already overstretched system would be swamped.

### What if we want an 'ideal' system?

If we are primarily screening for amblyopia we must remember that only a small number of people will be prevented from going blind each year and, therefore, the cost implications of screening are paramount. It would be possible to increase the number of orthoptists screening younger children. As refractive error is the greatest predictor of amblyopia,[6] it is essential that orthoptists should be well versed in the simple art of refraction: for almost unaccountable reasons they are not currently trained in this technique. Orthoptists, who are superbly trained in the handling of young children, would be able to carry out tests on selected children to determine their acuity, using methods such as forced preferential looking.

Photo refraction is an exciting technique under development that may be used by less fully trained personnel to detect refractive errors. There are difficulties with this in that techniques requiring a camera are expensive if Polaroid film is used, complicated if black and white film is used, and the capital cost of video photo refraction is high. Another problem is that the degree of training required probably means that the skills of an orthoptist are necessary. We should develop an 'at risk' concept for children with a family history, a history of squint, or refractive error.

It is difficult to be clear about the role of opticians in screening of vision The use of opticians for this is likely to be very expensive and to result in little reduction in visual handicap, but it is possible to see a role for them as the first point of referral after screening for the management of most refractive errors.

Interest is stirring among professional bodies and those concerned with community health and we can hope for a bright future in screening. This must be preceded, however, by careful nationwide planning, or we may be involved in enormous expenditure for little gain, which might never be rectified.

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# Top up transfusions in neonates

There are four reasons for giving top up transfusions to preterm infants: to replace acute blood loss; to replace chronic blood loss to treat hypotension, and to reverse the chronic anaemia that is characteristically seen at 7 to 8 weeks of age in preterm infants and earlier in survivors of haemolytic disease caused by blood group incompatibility.

## Replacement of acute blood loss

A neonate who has suffered an acute intrapartum haemorrhage or postnatal haemorrhage must have an immediate blood transfusion. Ideally, ABO and Rh compatible blood that is less than two days old (checked by an emergency cross match) should be given, but in an emergency fresh, uncrossmatched, O negative blood can be used. Transfusion should be continued until the systolic blood pressure is greater than 40 mmHg and the packed cell volume is 35–40%. This aspect of neonatal transfusion is not contentious.

## Replacement of chronic blood loss

A baby weighing 1000 g has a blood volume of 80 ml of which about 35 ml are red cells. His red cells have a shortened survival time and his erythropoietin production is suppressed.[1] Severe illness may cause red cell haemolysis and depresses the marrow. This is well recognised in sepsis,[2] and probably also occurs in ill hypoxic neonates on ventilators whose transfusion requirements considerably exceed their blood losses either haemorrhagic or iatrogenic. It is iatrogenic blood losses, however, that pose a major problem for the critically ill preterm neonate. Despite the use of transcutaneous or continuous $PO_2$ and $PCO_2$ monitors he may require a minimum of eight to 10 blood gas analyses per day, in ill hypotensive infants transcutaneous monitors are unreliable, umbilical artery catheters with a transducer in their tip do not measure $PaCO_2$ or pH, and all continuous recording devices require calibration. As well as blood gas measurements, sick babies have multiple blood samples withdrawn for haematological, biochemical, and serological analyses.

Blood gases may be measured on a 100 µl sample, and it is 20 years since Wilfrid Payne at the Hammersmith Hospital reported that he could do 10 biochemical investigations on 1 ml.[3] Many neonatal paediatricians, however, have to work with laboratory services that are at best covertly uncooperative, and at worse overtly hostile to requests for ultramicroscopic analyses with the quick turn round essential for neonatal intensive care. This can result in unnecessarily large volumes of blood being sampled from neonates.

Three approaches have been used to maintain adequate haemoglobin concentrations in the baby. Transfusion may be carried out when he has had the equivalent of 1% of his birth weight removed as blood—that is, 10 ml in the baby weighing 1000 g, or when he has had 10% of his blood volume removed—that is, 8 ml in the baby weighing 1000 g. Both approaches are equivalent to permitting the loss of about one pint of blood from an adult. Alternatively, the blood may be transfused when the baby's packed cell volume (PCV) drops below some preset point. Whichever approach is used, it usually results in the baby having blood transfused with the same frequency, and at about the same PCV—that is, 35–40% when he is given about 15 ml/kg of packed red cells. These practices, and in particular the cut off point for PCV of 35–40%, have never been evaluated in prospective randomised controlled trials and are based on two pieces of evidence, both of which I find convincing.

Firstly many clinicians feel that when the PCV in an ill baby weighing less than 2000 g falls below 35–40% the baby deteriorates (my own belief is that the danger point is nearer 40% than 35%). The baby may have increased apnoea, he may show signs of heart failure, develop a metabolic acidaemia, or his requirements for ventilatory support may increase. In addition, if the PCV is allowed to fall as low as 25–30%, the volume of blood required to increase the PCV to 40% introduces problems of vascular overload.

Secondly, the physiological justification for this approach comes from evaluation of the data on systemic oxygen transport and tissue oxygen extraction in the neonate.[4] There are three factors to be considered in systemic oxygen transport: cardiac output, PCV, and the position of the oxyhaemoglobin dissociation curve. The neonatal cardiovascular system is working at the limits of the Frank-Starling curve[5] and has little if any capacity for maintaining tissue oxygen delivery by increasing cardiac output in the presence of anaemia. In the neonate the ability of the tissues to extract oxygen from the blood is seriously compromised by the left shifted oxyhaemoglobin dissociation curve, and this is made worse if the baby is already hypoxic because of severe lung disease. Thus it is logical to keep the PCV in the optimal range. I know of no data about the optimal PCV in neonates, but in animals the cardiac output begins to increase once the PCV falls below 35–40%.[6] I have no doubt, therefore, that in the ill baby of very low birth weight the PCV must be kept above 35–40%.

## Hypotension

There is now a wealth of evidence that hypotension is bad for small babies. It is of clear aetiological importance in periventricular haemorrhage and periventricular leucomalacia,[7] necrotising enterocolitis, and renal failure. Hypotensive babies with respiratory distress syndrome are more likely to die.[8] The normal blood pressure in the babies most likely to require transfusion—that is those less than 32 weeks old and weighing less than 1500 g—averages 50–55/30–35 mmHg. Clinical experience suggests that the systolic pressure must be kept above 35–40 mmHg and the mean above 25–30 mmHg.

When hypotension is seen after birth it is commonly due to a low blood volume.[9] Later in the first week, hypotension may be due to volume depletion (blood sampling, dehydration), haemorrhage (from catheters, disseminated intravascular coagulation, or within the brain), drugs (tolazoline, pancuronium), or severe illness (sepsis). Furthermore, positive pressure ventilation can compromise venous return and cardiac function, and so it is particularly important to maintain a ventilated infant's blood volume.[10]

Although infusion of an inotropic drug such as dopamine can be valuable in severely ill babies, under most circumstances volume expansion is the appropriate treatment. For the reasons outlined above, if the PCV is less than 40% the transfusion should be given as blood (10–15 ml/kg), but if the PCV is over 40% a similar volume of plasma or albumin can be used.

## Late anaemia

By 7 to 8 weeks of age, the haemoglobin concentration in many babies of less than 1500 g in weight has fallen to 7–8 g/dl, and similar haemoglobin concentrations may occur even earlier in infants who have had Coombs' positive haemolytic disease of the newborn. By this age, in the absence of lung disease and in the presence of a rise in haemoglobin A concentrations, a shift to the right of the oxygen dissociation curve, and improved cardiovascular function, tissue oxygen delivery remains good even at haemoglobin concentrations of 7–8 g/dl.[4] If anaemia is accompanied by a good reticulocytosis ($>150\times10^9/l$) no treatment is indicated, in the expectation that the haemoglobin will rise spontaneously. If the haemoglobin falls below 7 g/dl, however, or if the infant feeds poorly, or is dyspnoeic at rest, 25–35 ml/kg of packed red cells should be transfused.[11]

## Risks of transfusion

Neonatologists must of course minimise the need for transfusion by asking laboratory colleagues to cooperate by providing adequate ultramicroscopic analytical systems. We should minimise iatrogenic blood loss by complementing arterial blood gas analysis with some form of continuous blood gas monitoring system, either intravascular or transcutaneous, although we must acknowledge the limitations of transcutaneous monitoring for preventing retinopathy of prematurity In particular, the occasional wildly inaccurate transcutaneous $PO_2$ measurement means that several arterial blood samples for blood gas analyses will be needed every 24 hours in babies at risk from retinopathy of prematurity.

Although cases of neonatal acquired immune deficiency syndrome (AIDS) related to transfusion have been reported,[12] they occurred before testing of donors for human immunodeficiency virus (HIV) antibody had become routine and before groups at risk voluntarily stopped donating blood. In the current furore about AIDS neonatologists must try and maintain a sense of proportion. The likelihood of a neonate acquiring AIDS from donor blood in the United Kingdom is remote: it has been estimated at less than one case in 1 000 000 transfusions.[13] This is less than the risk of developing or dying from hepatitis,[14] or contracting cytomegalovirus infection from the donor blood,[15] and much less than the risk of a baby weighing 1000 g dying if the systolic blood pressure and packed cell volume are allowed to remain below 40 mmHg and 40%, respectively. Indeed, for the past five years a much greater priority for neonatologists should have been to obtain donor blood that was free of cytomegalovirus infection rather than free of HIV.[16]

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# Environmental neonatology

Nowadays, the small or sick newborn baby is subjected to more intrusive and vigorous investigations and treatment than ever before in neonatal care.[1] The impressive fall in neonatal mortality of very low birthweight infants in the past decade has been welcomed. Concern has been expressed, however, that the development and application of new medical technology have outpaced considerations for the psychological well-being of the very young patient in hospital.[2]

## Crucial questions

Environmental neonatology is a multidisciplinary field concerned with the systematic study of special care facilities for the newborn and their impact on the medical and developmental state of sick infants.[3, 4] The crucial questions are: what is the environment of the special care baby unit like today, and how can we best provide for the bio-behavioural well-being of the preterm infant?

## Noise pollution

British safety standards require that the mean noise levels inside an incubator should not exceed 60 decibels. Particular life support equipment, however, and notably, the incubator alarm buzzer, occasionally exceed these limits (up to 85 decibels).[5] The risk of hearing loss in infants in the absence of other severe neonatal complications is negligible.[6] In contrast, sudden loud sounds often lead to adverse physiological effects in the newborn. These include sleep disturbance, motor arousal and crying, hypoxaemia, tachycardia, and increased intracranial pressure.[7] The latter may contribute to the development of intraventricular haemorrhage due to the poor autoregulation of the baby's haemodynamic state, and inadequate cerebral bloodflow in preterm infants.[8] Particularly loud impulse sounds are caused by the closing of incubator doors (up to 115 decibels sound pressure level), knocking or striking the isolette, or by placing bowls on the incubator.[4] Noise pollution is mainly caused by staff, and by inconsiderate placement of sound sources—for example, the telephone.[7] Low frequency sounds of less than 500 Hz are most likely to penetrate the incubator, masking the human voice and speech.[9] It is difficult to locate a sound source from the enclosure of the incubator, and the infant is prevented from learning the integration of a particular sound—for example, a voice—with a particular face—for example, the mother. The infant has no control over noise exposure.

## Ambient light exposure

The intensity of light in the hospital neonatal intensive care unit has increased five to tenfold in the past two decades.[10] Light intensity is about 60–90 footcandles[10] or 200 lumen/$m^2$.[11] Considerably brighter light comes from sources such as heat or phototherapy lamps, or sunlight. Infants in special care baby units are often exposed to such intensity for 24 hours a day. Surprisingly, little is known about the effects of light exposure on the small infant. 'Normal' neonatal intensive care unit light, however, may damage the retinas of extremely low birthweight babies.[10]

## Handling

On average, preterm neonates in special care baby units are handled 130 times every 24 hours.[12] The rest periods between handling are only 4·6 to 19·2 minutes. The main 'disturbers' are the nursing and support staff, then the paediatrician, and lastly, the parents. Handling has been found most consistently to cause disruption of infant's sleep patterns[13] and to lead to a higher incidence of hypoxaemia, bradycardia, apnoea, and behavioural distress.[4] A recent study reported that 83% of all incidences of hypoxaemia, 93% of bradycardias, and 38% of apnoeas, had occurred during or immediately after routine handling of preterm infants.[14] The most uncomfortable procedures are routine endotracheal suction and chest physiotherapy. Parental handling is mostly benign and usually consists of gentle stroking and talking which helps babies to settle or maintain deep sleep.[14]

## Daily rhythms and deep sleep

In most intensive care units there is no clear pronounced diurnal rhythm in noise and light intensity and staff activities.[15] This lack of day and night cycles may be responsible for delayed onset of periodicities and sleeping problems in preterm infants.[16] The introduction of reduced noise, light, and handling at night in neonatal intensive care units seems beneficial. Infants spent longer sleeping, less time feeding, and they gained more weight after being discharged home.[11]

High light and noise intensity and frequent handling not only lead to the disturbance of the infant's rest but also increase the time the preterm baby spends in rapid eye movement (REM) sleep. Lower tissue oxygenation, increased chest wall instability, and periodic breathing with the occurrence of five to 14 times more apnoeic episodes during REM sleep in comparison with deep non-REM sleep have been reported.[7]

## Early learning

The term 'infancy' derives from the Latin 'infans' which means 'speechless'. Young infants have no verbal language apart from crying, and learn through sensorimotor experiences and by making associations with stimuli.[18] Sensorimotor experiences are exposures to tactile and kinaesthetic, auditory, visual, motor, and vestibular information. The description of the current special care baby unit environment shows that there is little opportunity or support for early learning. Indeed, many of the sensorimotor experiences are unpleasant. Furthermore, fewer nurses have to look after more patients in postintensive care rooms. While the preterm infant's capacities for social interaction increase during incubation, vocal and visual stimulation from the nursing staff seem not to change, and are restricted to brief and functional routine contacts (MJ Tanke *et al*, abstract presented at 4th International Conference on Infant Studies, New York, April 1984). Knowledge of the long term effects of the environment of the special care baby unit on the infant is still limited. The observed problems in social interaction in preterm infants after discharge are likely to be consequences of the complex interactions of neonatal medical problems and the special care baby unit environment.[19]

## Implications for neonatal care

The reviewed evidence suggests that the preterm baby is not under or overstimulated, but inadequately stimulated while in hospital. The premature neonate is neither similar to the fetus nor to a deficient full term infant, but is a unique organism—a medical artefact with special needs.[4] There is no universal easy recipe for optimal psychological care, but there is a universal principle: individual care. This can be achieved as follows. Firstly, observe the baby before, during, and after procedures; how does he or she react? Secondly, design an individual plan of care to reduce stress and pain, and be supportive of the infant's own behaviour regulation; and thirdly, grow up with the patient. Care plans should adapt to developmental changes in infants' abilities.

Specific beneficial changes in the enviroment of the special care baby unit are reduction of noise and light intensity—for example, flexible lighting—reduced and more effective timing of procedures requiring handling, introduction of day and night differences, stroking, containment of motor activity after painful procedures, and sensitive social interaction with the more robust preterm infant.[4]

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## *Original articles*

# Clinical aspects of X-linked hypohidrotic ectodermal dysplasia

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SUMMARY Boys with X-linked hypohidrotic ectodermal dysplasia and their families were studied. Many suffered severe illness in early childhood and nearly 30% died; many had feeding problems, severe fever, atopic disease, and recurrent respiratory infections. Some infants failed to thrive. We found no consistent common endocrine or immunological abnormality, although most had abnormal immunoglobulin production. This may be related to the abnormal mucosa of the gastrointestinal and respiratory tracts which exacerbates the chronic obstructive airways disease found later in life in those who smoke. Mental handicap was not a feature, although convulsions sometimes occurred during fever.

Early diagnosis is important to avoid attacks of severe fever and so that rational management may be planned for other problems that arise. Dental advice should be sought before school age and genetic counselling may also be required. Many female carriers may be recognised at clinical examination: their affected sons can then be diagnosed more readily.

Hypohidrotic (anhidrotic) ectodermal dysplasia (HED) is characterised by the diminution or absence of eccrine sweat glands, by oligodontia and peg shaped teeth, and by hair that is sparse and thin. It is of interest to paediatricians because the substantial mortality and morbidity that are associated with it are manifest principally in young children. Early diagnosis—that is, before the condition becomes obvious—may also improve outcome.

The sex linked pattern of inheritance for HED was first described by Darwin in 1844.[1] The gene locus is now known to be on the proximal part of the X chromosome long arm, and gene localisation using deoxyribonucleic acid (DNA) probes is now progressing rapidly.[2] Male infants with HED are known to be at risk of severe fever[3] and anecdotal reports have been published of cases who have been mentally retarded, possibly as a result of their high fevers.[4] Their increased risk of chest infection and of atopic disease is also well recognised.[5]

This study reports the clinical findings from a survey of the disease that began in mid 1985. We have tried to determine the range of severity, in particular the mortality among affected male infants, and to pursue three lines of inquiry initiated by previous workers. The possibility of a primary immunological defect was investigated, the previous finding of low serum concentrations of parathyroid hormone was examined,[6] and methods of identifying female carriers of the gene were evaluated.

## Methods

Letters were sent to almost all hospital paediatricians, dermatologists, and clinical geneticists listed in the *Medical Directory,* and to many hospital dental surgeons. We asked them to notify us of any cases they knew of and for permission to contact the families concerned. We sought and obtained the consent of each family's general practitioner or dentist where appropriate, before contacting the index case. Families were visited at home, and the affected boys and possible carrier female subjects were examined. Measurements of height, weight, and head circumference were taken, and the chest, skin, and nails were examined.

Where possible, blood samples were taken for use in a concurrent genetic linkage study with DNA probes and for immunological and endocrinological investigations. Finger tip impressions were taken in Permelastic light body impression material (Sybron/Kerr) by spreading the mixed material on the subjects' finger pads, immersing them in warm water, and then peeling the impressions off with adhesive tape.[7] These were stored on microscope slides in racks and subsequently examined under a dissecting microscope at a magnification of 10.

Sweat tests were performed on the backs of definite and possible carrier female subjects: iodine in spirit was painted over as large an area of the back as possible. This was allowed to dry and then covered with a layer of corn starch in oil applied as evenly as possible. The subject was then asked to sit near a fire until she became hot. The pattern of sweating shown on her back by black dots over the active sweat pores was then noted.[8]

Immunoglobulins G, A, and M were measured by radial immunodiffusion, IgE by radioimmunoassay and IgG subclasses by semiquantitative simple immunodiffusion. Antibodies to the commensals *Escherichia coli* and *Candida albicans* were detected by haemagglutination[9] and immunofluorescence, respectively. Total classical and alternative pathways of complement, lymphocyte surface markers, and α- and γ- interferon production by peripheral blood lymphocytes were measured as previously described.[10 11] For neutrophil chemotaxis, an 'under-agarose' method was used with N-formyl-L-methionyl-L-leucyl-L-phenylalanine as chemotaxin.

Serum parathyroid hormone was measured by a new immunochemiluminometric assay specific for the intact 1–84 peptide.[12] With this assay all normal subjects have detectable circulating concentrations. The intact peptide corresponds to the circulating biologically active peptide and provides an assessment of parathyroid secretory activity that is probably superior to the conventional radioimmunoassay.

Prolactin was measured by a radioimmunoassay technique using Chelsea reagents provided by Keith Ferguson of the Chelsea Hospital for Women. Thyroid stimulating hormone was measured using a monoclonal tracer supplied by Serono, and antisera for the solid phase was supplied by the Scottish Antibody Production Unit and measured by the automated method of John and Jones.[13] Free thyroxine (FT4) was measured by radioimmunoassay, using a commercial kit (Amerlex Free T4 Kit, Amersham).

## Results

We contacted 56 families with some form of hypohidrotic ectodermal dysplasia. Of these families, 22 had more than one affected subject, and the inheritance in all the families was compatible with X-linkage. Another 12 families had only one affected subject, but there was firm evidence of sex linked inheritance because the mother of the affected subject showed several features of the condition and there were often several such related female carriers. The remaining cases, although some were probably examples of the X-linked form, were excluded from the study.

The phenotype of X-linked HED (fig 1) has been well described, and we have no new findings. The boys had sparse scalp and body hair, only a few teeth which were peg shaped (figs 2 and 3), and diminished or absent eccrine sweat pores. The mean number of erupted teeth of the deciduous and permanent dentitions in the male subjects was six. Over 30% had abnormalities of the breasts (absent, simple or accessory nipples) and over 30% had 'simple' ears (bat ears, satyr ears, or absence of some folds). As others have reported, we commonly found wrinkling and pigmentation around the eyes.

Sweat pores were usually absent from the finger tips of most of the men in this series (fig 4), though several men in two families showed appreciable, although still subnormal, numbers of sweat pores. There was no doubt about the mode of inheritance in either family. Twenty seven of 50 infants (54%) suffered recurrent fevers; some boys were intolerant of cold, possibly related to their lack of subcutaneous fat.

### SEVERE ILLNESS IN EARLY CHILDHOOD

The mortality in early childhood was assessed by

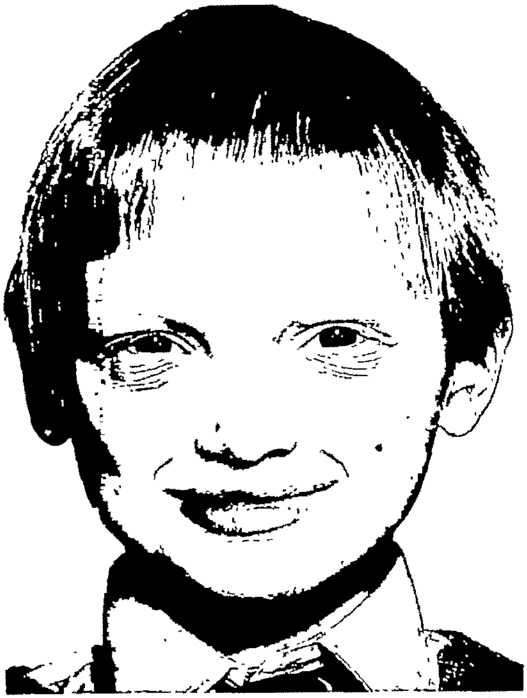

Fig 1 *Nine year old boy with hypohidrotic ectodermal dysplasia*

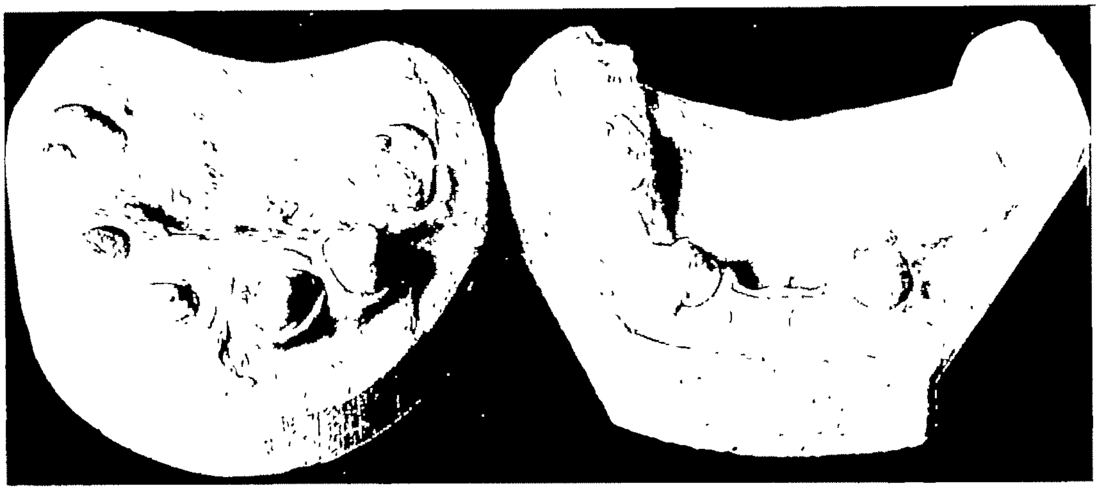

Fig 2 *Dental models of upper (L) and lower (R) jaws of boy aged 7*

Fig 3 *Dental radiograph of affected boy aged 14*

considering the 22 families with more than one affected male subject. The family tree was drawn as far back as eye witnesses could distinctly recall, and male subjects were included if there was reliable information about their health in childhood. The index case in each family was excluded from this analysis. The table shows the mortality nine of the 12 deaths occurred in infancy; two deaths in the second year; and one death at 2½ years Neonatal deaths did occur, as in the two index cases. Of the 12 deaths, three occurred in the 1940s, three in the 1950s, one in the 1960s, four in the 1970s, and three have occurred so far in the present decade. Notably eight of the deaths occurred in the elder of two affected brothers, and only two boys died who were the younger of two affected brothers This shows

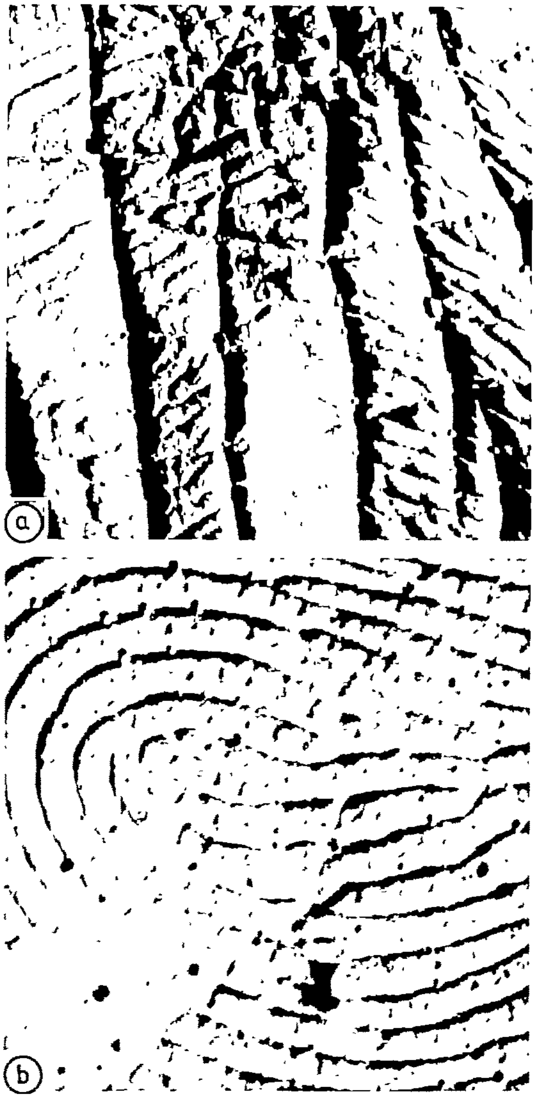

Fig 4 *Finger impressions of affected boy (a) and normal adult (b)*

that early diagnosis—whether by physician or by family improves the outcome for these boys.

If doubt is cast on these figures (in case the diagnosis in some cases was suspect) a similar conclusion can be reached by considering the infant mortality of the 88 male subjects born to the obligate carriers whom I met in this study; of these 88, 20 died in infancy This gives a mortality varying from 23% (if affected boys are no more likely to die than their normal brothers) to 45% (on the assumption that all the normal boys survive)

Table *Complications of HED in early childhood*

| *Complication* | *No (%)* |
|---|---|
| *First year* | |
| Mortality | 9/43 (21)* |
| Severe non-fatal illness | 14/49 (29) |
| Total with episodes of severe illness | 25/58 (43) |
| *Years 0–3* | |
| Mortality in years 0–3 | 12/43 (28)* |
| Severe non-fatal illness | 18/51 (35) |
| Total with episodes of severe illness | 32/65 (49) |
| *Other complications in survivors* | |
| Eczema | 39/55 (71) |
| Asthma or recurrent wheezing | 35/54 (65) |
| Nasal crusting | 42/53 (79) |
| Recurrent fevers in infancy | 27/50 (54) |
| Recurrent upper respiratory tract infections in childhood | 21/47 (44) |
| Feeding problems in infancy | 32/47 (68) |
| Specific allergies (to foods or drugs) | 14/53 (26) |

*Mortality figures exclude index cases

The figures for severe illness in early childhood in the same table relate to all survivors about whom we had clear information concerning their childhood (whose parents were available for interview) These illnesses commonly comprised prolonged high fevers in infancy often accompanied by chest infections and failure to thrive. All these children were admitted to hospital and were given intravenous fluids. Many of them spent several months of the first year in hospital. In the table the data on mortality and illness are combined to give the risk of an affected boy having a severe illness, fatal or otherwise.

### NUTRITION AND GROWTH

Thirty two of 47 boys (68%) had feeding problems and 19 had some degree of failure to thrive. The feeding problems comprised apparent lack of interest in feeding or a frank inability to feed despite good effort. Forty two of 53 infants (79%) had nasal obstruction caused by the accumulation of dried crusts in the nasopharynx and this may have prevented adequate sucking. A few infants required tube feeding for weeks or months Sixteen of 49 boys (33%) had problems chewing specific foods such as nuts and tough meats when older even with dentures Thirty one of 50 male subjects (62%) produced insufficient saliva and hence required fluid to swallow dry foods. Nine of 53 (17%) were also allergic to specific foods.

Affected male subjects tended to be of below average stature, weight, and head circumference, with about 10% being more than two standard deviations below the population mean for these characteristics. This was most noticeable in the first few years, when general health was poorest. Four infants were below the third centile for weight at birth; the two who are now adult are above the twenty fifth centile for height and weight, and one of the boys, now aged 3, has caught up to near the tenth centile. The other boy remains below the third centile at 9 years; he had a Wilms' tumour removed and subsequent chemotherapy. A boy aged 14 remains below the third centile for no apparent reason. Two brothers with HED are below the third centile for height and the tenth centile for weight at 3 and 15 months of age; only the elder boy had feeding problems.

### ATOPY AND CHEST DISEASE

Thirty nine of 55 boys had eczema in childhood; this tended to become less severe with age. Thirty three of 54 also gave a history of recurrent wheezing typical of asthma, and a further two cases (included in the table) had audible wheezes on examination. This indicated a high incidence of atopy. The association of HED with chronic chest disease was noted by Beahrs *et al*, and is probably the result of deficient mucus production by the respiratory epithelia in the trachea and bronchi as well as in the nasopharynx.[5] Three male subjects in the families described here died of chronic obstructive airways disease in their sixties, during the past 3 years. All three men were heavy smokers and had either lived or worked in areas with industrial dust pollution; One had died from pneumonia aged 28 years

Assessment of humoral immunity was performed in 36 affected male subjects, 25 of whom had distinctly abnormal results and a further two of whom had marginally abnormal immunoglobulin concentrations; no consistent primary defect was identified, however Ten of 36 had raised IgG concentrations, some as high as 48 g/l, and three subjects had low concentrations. IgM concentrations were raised in three cases and reduced in six, although the reduction was marginal in most of them. Eight subjects had definitely low IgA concentrations, and in one case it was marginally low. IgE was considerably raised in most, a few having concentrations of >1 g/l; in all, 19 of 28 tested had raised concentrations.

None of the patients lacked any IgG subclass. Normal titres of antibody to the commensals *E coli* and *C albicans* were present in all but one patient. This child, who lacked antibodies to *C albicans,* was almost 4 years of age when tested: the organism is widely distributed and antibodies to it are usually evident by the age of 6 months.

The complement system, both classical and alternative, was assessed by haemolytic assay and found to be normal in all seven patients tested. Peripheral blood leucocyte and lymphocyte counts were normal in 25 cases. Because of transport problems, tests of cellular immunity and neutrophil function had to be restricted to a smaller number of patients. T cell numbers were assessed in eight male subjects and subsets were normal in six. In two boys the T8 (suppressor) class was marginally raised compatible with a minor viral infection. All cases were clinically well when the blood was taken for leucocyte function tests. Alpha and $\gamma$ interferon production was normal in the six cases tested. Neutrophil chemotaxis was measured in four cases and nitroblue tetrazolium reduction in eight, with normal results in all cases.

Thyroid function was measured in 25 cases and the free thyroxine concentration was normal in each case. The thyroid stimulating hormone concentration, however, was raised in two boys at 6·6 and 9·7, respectively The prolactin concentration was normal in the first boy but was marginally raised (at 455 mU/l) in the second, raising the possibility of a more generalised hypothalamic dysfunction. Both these boys were above the fiftieth centile for height, weight, and head circumference and doing reasonably well at normal school. Prolactin assays were performed in 19 other cases and yielded normal results.

Parathyroid hormone assay measuring intact parathyroid hormone was performed on serum taken from 22 of the affected male subjects. Only one value was far from the normal adult range of 0·96–9·8 pmol/l, being 39·6. Excluding this case, for which we have no explanation at present, the mean, range, and standard deviation of the cases of HED were 2·58, 0·85–9·50, and 1·95 pmol/l, respectively. These do not differ significantly from (adult) normal values. A previous report mentioned a tendency for the parathyroid hormone concentration to be low in cases of HED,[13] but the assay method was not specified and was probably a traditional radioimmunoassay for the C terminal of parathyroid hormone and not for the intact protein Serum concentrations of calcium and phosphate, and alkaline phosphatase activity were normal in that report; we did not measure them in our cases

### CONVULSIONS AND DEVELOPMENT

Three of 50 boys had convulsions in childhood, and a further two boys may have done so. No adults had any such episodes. We outline the case histories as follows.

Case 1 had a prolonged high fever at 10 weeks of age, with multiple seizures and he developed a spastic cerebral palsy. Although his intellect was difficult to assess, his mental development seemed to be less impaired than his physical defects initially suggested. His development before this illness was unremarkable.

Case 2 had a fever at 2 weeks of age, with two brief convulsions, then no further episodes. When last seen he was functioning well at a normal secondary school and had no apparent sequelae.

Case 3 had an isolated convulsion when otherwise well during the investigation of polyuria at the age of 4 years. Such polydipsia and polyuria may be used as a mechanism for controlling body temperature during a severe episode of illness at 9 months.

Case 4 had high fevers and may have had a brief febrile fit.

Case 5 had a similar history to that of case 4, occurring at 2 months; neither had a convincing history of convulsions and neither child suffered adverse sequelae.

Of the 50 cases for whom we had adequate information about their childhood, in 10 some concern was expressed about the child's development. One child had cerebral palsy (case 7), and he attends a school for the physically and mentally handicapped. One child attends an ESN (M) class, and his development has been generally retarded. He suffered severe illness during his first 2 years, although he is not thought to have had convulsions. The other eight children all developed normally and did well in normal schools, but they had some early difficulty with speech or hearing, or both, which subsequently resolved. Another two boys received preschool speech therapy.

Seven of 38 boys had additional school problems; four were plagued by teasing at school. They were called names such as 'Dracula' or 'Fang'. This problem was worse in secondary schools than in primary schools, and could have assumed major proportions in adolescence. The three remaining boys had all missed substantial periods of school because of ill health and had work to do to catch up. In one case this necessitated temporary placement in a remedial class.

Of the adults seen, none was handicapped except by heat intolerance. The range of occupations undertaken by men with HED is wide, ranging from technical, managerial, and academic positions to manual labour. One labourer fainted in a heat spell, and several men have been unable to tolerate very hot industrial work. There are insufficient adults in this series to see if HED is significantly associated with any particular pattern of employment, but our strong impression is that the range of occupation is limited solely by heat intolerance. The ability to tolerate hot conditions varies among individuals, and the male subjects in certain families have few symptoms: they include those who have appreciable numbers of sweat pores.

FEMALE CARRIERS

Fifty seven obligate carrier female subjects in 22 families were interviewed and examined. Some displayed no features of the condition, a few resembled the affected male subjects, while most displayed a few of the features. Symptoms of hypohidrosis were generally not severe, but 26% complained of heat intolerance and 46% had noticed that they sweated less than normal. Some of the carriers had feeding difficulties similar to those of the boys in early childhood and had also had recurrent chest infections, but these were never as severe as in the men. Eighteen per cent described themselves as 'chesty' and nineteen (79%) of the 24 who tried to breast feed their infant(s) reported an insufficiency of milk.

The permanent teeth were examined by us or described by the woman herself in 46 cases, and 36 of these women (78%) had distinct dental abnormalities. These comprised absent permanent teeth, often associated with the persistence of deciduous teeth, small teeth resulting in gaps between the teeth, and peg shaped teeth. The deciduous teeth were described as having been abnormal in seven of the 15 women who could clearly recall their milk teeth with absent, peg shaped, or small teeth. This was borne out by examination of three young girls who were confirmed carriers, all of whom had some small or absent teeth. Thirty nine of 54 confirmed carriers (72%) described their hair as being sparse, or fine, or both. Their eyebrows were also often thin, sometimes being particularly sparse over the lateral third.

The sweat tests performed on 37 confirmed carriers were positive in all but one case (97%), showing distinct patches of anhidrosis. In a few cases only these followed the lines of Blaschko. It is important to be familiar with the appearance of the normal back when performing this test, so as not to overinterpret normal variation in the distribution of sweat pores. Sweat tests were also performed on the backs of 29 definite gene carriers whose teeth were unequivocally abnormal; the sweat test was positive in 28 cases.

## Discussion

The natural history of HED varies among subjects and perhaps between families, but it does follow a pattern Most of the boys have problems as infants with difficulties in feeding or episodes of severe illness, or both, often of severe fever associated with infections such as pneumonia. As long as the boys are subject to ill health concern is expressed about their growth and development.

Those boys who are breast fed may receive inadequate milk from their mothers who will usually be carriers of the condition: these women are often unable to breast feed their infants, although some do so perfectly well. When advising the mother of a bottle fed infant it is useful to suggest that she does not heat up his bottle, heating can make it less palatable and contribute to his overheating

At some stage from the age of 1 to 4 years most affected boys will abruptly, and for no obvious reason, show an improvement in their general condition. They are no longer subject to serious illness, they feed well, and they grow and develop normally They may, however, remain susceptible to recurrent upper respiratory tract infections, bouts of fever, eczema, asthma, and food allergy They may require water to drink with meals and need artificial tears because of inadequate salivary and lachrymal secretion. They will almost certainly require dental attention and artificial dentures. They may be bothered by teasing at school and self consciousness during adolescence They are unlikely, however, to fall seriously ill. Heat intolerance does occur in older boys but can be dealt with by taking cool drinks and wearing wet T shirts.

Previous reports of mental retardation have exaggerated the problem, probably through a reporting bias; we found no evidence of mental retardation as a primary feature of the disease. The one child in our series with cerebral palsy was much less retarded mentally than he was physically, and his handicap was probably due to his fits at the age of 10 weeks. Only one other child had an appreciable educational problem and this did not constitute evidence of mental deficiency.

To what extent the abnormal conformation of the airway—the nose and the mouth with the oligodontia—may contribute to speech problems is not clear. It may be that artificial dentures have a role in assisting the boys' speech development, whether dentures help acoustically or serve to boost confidence among peers is not clear. Many boys are eager to wear dentures from the age of 3 or 4 years and this can be safely encouraged; upper dentures, at least, are often tolerated from this age. They may help with eating as well as boosting confidence and aiding speech.

Hearing may be mildly and transiently impaired by the crusts of dry wax that accumulate in the external auditory canal and perhaps by blockages in the eustachian tubes.

The results of immunological function tests showed a scatter of disorders, especially in humoral function, but no consistent anomaly. This pattern could be generated by secondary effects of the recognised defects in mucosal integrity and function. The respiratory and gastrointestinal tracts are defective in mucus production and may therefore permit the passage of excessive quantities of foreign material leading to dysregulation of the immune system. The defective mucus production in the respiratory tree probably contributes to the chronic obstructive airways disease that may develop in male subjects who smoke and who also work in a dusty atmosphere.

Immune function tests were only performed in survivors. The possibility therefore exists that those who succumb in early childhood do have a more severe immune disorder, perhaps a disorder of cell mediated immunity We did not test delayed hypersensitivity reactions, and these have been shown to be impaired in some male subjects with HED.[14] We also did not test enzymes in the pathways of DNA biosynthesis in phytohaemagglutinin stimulated lymphocytes, as has previously been done.[15] The finding of reduced activities of these enzymes in patients with a diverse range of immune defects is difficult to interpret; only one patient with HED was tested. The comparison in that paper was with normal subjects rather than with cases of atopy or chronic sepsis, and similar findings were made in one patient with a high concentration of IgE. There is certainly no reason to suppose that the finding was related to the primary defect in HED.

Thyroid anomalies have been described in cases of hypohidrotic ectodermal dysplasia,[16] although not necessarily in X-linked HED. It would seem prudent to monitor the growth of boys with HED and to investigate those with short stature so as to detect endocrine or other treatable causes of this problem. We did not confirm the previous report of low parathyroid hormone concentrations in these subjects.[6]

Most female carriers of HED are recognised by dental anomalies, and most of those whose teeth are normal may be recognised by their abnormal pattern of sweating. Asking for symptoms of HED and looking for sparse scalp hair were found to be too subjective to identify carriers accurately. The dental and sweating signs are useful because they can be applied to female relatives to modify the recurrence risk that is given to them after the birth of even one affected child in a family. It is hoped that DNA probe analysis of the gene will permit still more accurate counselling in the future. When an affected infant is anticipated it may be that his early management is improved so that he is less likely to succumb to infection or severe fever.

After childhood the practical problems of living with HED steadily lessen The subject with HED and his family, however, would be particularly foolish to smoke. He would also be well advised to avoid a hot or dusty atmosphere at his place of work.

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# Hypoxaemia in wheezy infants after bronchodilator treatment

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SUMMARY The response of the bronchi to nebulised salbutamol was measured in five recurrently wheezy infants. Changes in oxygenation (measured by pulse oximeter and transcutaneous $PO_2$ electrodes) and carbon dioxide (measured by transcutaneous $PCO_2$ electrode) were recorded at the same time. Neither nebulised saline nor salbutamol caused any changes in the measurements of airway function. A significant drop in mean oxygen saturation of 2% and of transcutaneous oxygen tension of 1·3 kPa occurred after nebulised salbutamol. No significant change occurred in measurements of transcutaneous carbon dioxide tension, nor was there any significant change in any of these measurements after 2·5 ml of nebulised saline had been given as a control. These results suggest that nebulised salbutamol may cause significant hypoxaemia, in wheezy infants probably by inducing ventilation/perfusion disturbance.

Nebulised selective $\beta_2$-adrenoceptor agonists are still used in the treatment of wheezing in infants in spite of the evidence that they may be ineffective [1-3] Recently they have been shown to cause deterioration in peripheral airways function in this age group.[4,5] Because the techniques used for measuring peripheral airway function in wheezy infants are new,[6,7] it may be that any deterioration noted was artefactual.

In adults and older asthmatic children transient but significant hypoxaemia after treatment with selective $\beta_2$-adrenoceptor agonists has been reported despite improvement in airway patency.[8-10] This may be the result of a disturbance in ventilation/perfusion balance brought about by pulmonary vasodilatation If a similar imbalance occurs in the infant lung, without bronchodilation severe hypoxaemia could result.

We assessed the changes in airway function and blood gas measurements after giving nebulised salbutamol to wheezy infants and compared them with a group given nebulised physiological saline.

## Patients and methods

Five recurrently wheezy infants (mean age 10·4 months, range 6–15) were studied. They were sufficiently disturbed by wheeze to justify assessment with a view to nebuliser treatment at home. All were wheezy at the time of testing The reproducibility of the response to salbutamol was assessed two weeks later in four of the infants. The fifth infant did not have a repeat study because he developed severe bronchoconstriction after the initial treatment with salbutamol.

Sedation with chloral hydrate (100 mg/kg orally) was given 30 minutes before each test. No infant had received any bronchodilator within 24 hours of the test. Ethical committee approval and parental consent were obtained for all studies.

### PROCEDURE FOR SALBUTAMOL CHALLENGE

When asleep the infant was placed in a whole body plethysmograph, and baseline measurements of thoracic gas volume and inspiratory airway resistance were made.[11] From these, their multiple specific airway resistance was calculated. Partial expiratory flow volume curves were then calculated by suddenly inflating a snugly fitting thoracoabdominal jacket at the end of a tidal inspiration, thus causing forced expiration.[6,7] From the flow signal measured through the face mask by the screen pneumotachograph and its integral (volume), a partial expiratory flow volume curve was constructed, and the maximum flow at a lung volume corresponding to functional residual capacity was computed. Six to eight of these manoeuvres were carried out to obtain a mean baseline value for the maximum flow at functional residual capacity ($\dot{V}$maxFRC). Reference values for airway resistance and $\dot{V}$maxFRC were obtained from previously reported data.[12 13]

The face mask was removed and 2·5 ml physiological saline at room temperature was given through a Turret nebuliser (Medic Aid) driven by compressed air at 6 l/minute; nebuliser output was directed over the nose and mouth of the sleeping infant, and the nebulisation time was about five minutes. A further set of partial expiratory flow volume curves was then obtained after replacing the face mask and waiting for the baby to settle for five minutes.

After a 20 minute interval 2·5 mg of preservative free salbutamol sulphate in 2·5 ml physiological saline (one Ventolin Nebule) was given by jet nebuliser as described above and further sets of flow volume curves obtained 20 minutes later.

### RECORDINGS

Transcutaneous $PO_2$ ($PtcO_2$) was monitored using a transcutaneous electrode (Kontron Cutan 820) heated to 44°C and placed on the lower leg after calibration in air. Transcutaneous $PCO_2$ ($PtcCO_2$) was monitored using a transcutaneous electrode (Radiometer TCM 20) heated to 43°C and placed on the lower leg after calibration in 10% carbon dioxide. Readings of $PtcO_2$ and $PtcCO_2$ were taken after a stabilisation period of 15 to 20 minutes. A pulse oximeter (Ohmeda Biox 3700) was used to measure arterial oxygen saturation ($SaO_2$) and heart rate. Data were recorded only when the pulse signal was satisfactory.

Values of $SaO_2$, $PtcO_2$, $PtcCO_2$ and heart rate were recorded in the five minutes before and throughout the challenge procedures, and for 20 minutes after the saline and salbutamol had been given. For statistical purposes, comparisons were made between the mean values during the five minute interval before nebulisation and those measured during 0–5 and 15–20 minutes after nebulisation. The paired *t* test was used to test the significance of differences in results after treatment with salbutamol and with saline.

## Results

The results for the two study days were similar, with no significant differences between days. Where two sets of data were collected, mean values were used giving one set of results for each of the five patients.

Baseline measurements of lung function indicated that there was definite airway obstruction, the mean (SD) value of specific airway resistance was 249 (106)% of the reference value[12] and the $\dot{V}$maxFRC was 24 (8·4)% of the reference value.[13] Baseline values of $PtcO_2$, and $PtcCO_2$ before giving the saline (table) reflect the errors inherent in methods of

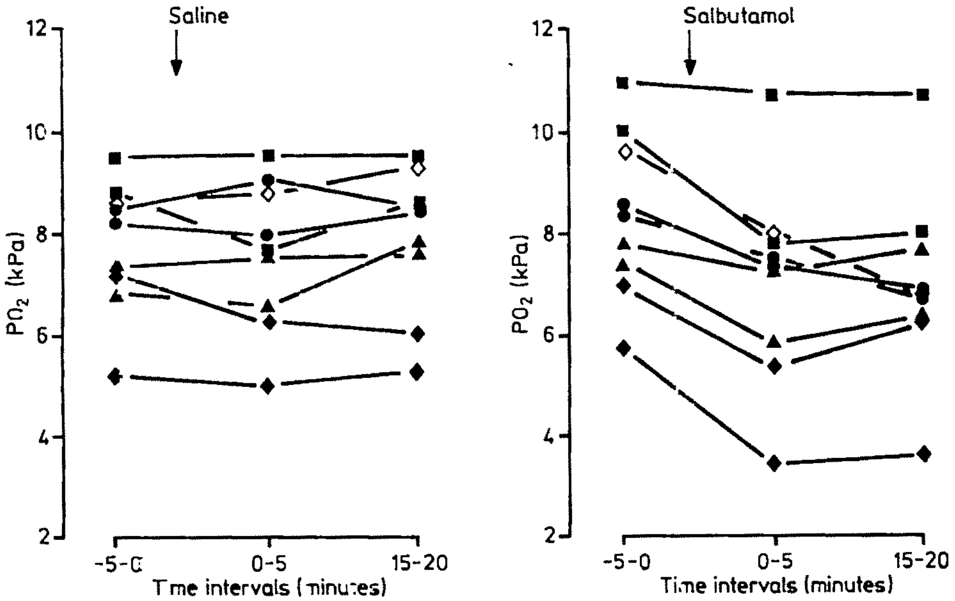

Figure *Changes in peripheral transcutaneous $O_2$ before and after nebulised saline and salbutamol Each point represents mean value over each five minute interval for four infants studied on two occasions each (closed symbols) and one infant studied only once (open symbols).*

Table *Mean (SD) values of $\dot{V}$maxFRC, heart rate, oxygen saturation, transcutaneous $PO_2$, and transcutaneous $PCO_2$ in the five minute intervals before and after nebulised saline and salbutamol*

| | *Nebulised saline* | | | | *Nebulised salbutamol* | | | |
|---|---|---|---|---|---|---|---|---|
| | *Before Mean* | *(SD)* | *After Mean* | *(SD)* | *Before Mean* | *(SD)* | *After Mean* | *(SD)* |
| VmaxFRC (ml/sec) | 24 | (8·4) | 25 | (6·5) | 26 | (6·5) | 25 | (11·1) |
| Heart rate | 133 | (15) | 132 | (14) | 135 | (17) | 151 | (14)* |
| Oxygen saturation (%) | 86 | (5·6) | 86 | (5·4) | 87 | (6·7) | 85 | (7·0)* |
| Transcutaneous $O_2$ (kPa) | 7·8 | (1·1) | 7·7 | (1·2) | 8·5 | (1·5) | 7·2 | (1·6)† |
| Transcutaneous $CO_2$ (kPa) | 58 | (4·1) | 57 | (4·1) | 56 | (3·4) | 55 | (3·9) |

Before and after salbutamol *$p<0·01$ †$p<0·001$

transcutaneous measurement. The mean value of $SaO_2$ was significantly lower than normal in these supine, sedated, wheezy infants.

Significant falls in both $PtcO_2$ ($p<0·001$, figure) and $SaO_2$ ($p<0·01$) occurred within five minutes of giving of nebulised salbutamol, but not after saline (table). The lowest values of $PtcO_2$ (6·6 kPa) and $SaO_2$ (84%) occurred at a mean time of 11 minutes after the end of nebulisation. Twenty minutes after the end of nebulisation the mean value for $PtcO_2$ of 7·1 kPa was still significantly lower than the mean value of 8·5 kPa before salbutamol ($p<0·01$), although the $SaO_2$ had returned to the baseline value

There were small changes in $PtcCO_2$ measurements. The small decline after salbutamol had been given was not significant (table). Mean heart rate increased significantly after salbutamol was started, the increase persisting for at least 20 minutes after nebulisation had stopped. There was no significant change in heart rate with nebulised saline.

## Discussion

We found a significant deterioration in oxygenation in wheezy infants after they had been given salbutamol. These changes were similar to those reported in older asthmatic children and adults.[8–10] There was a small decline in $PtcCO_2$ in conjunction with the hypoxaemia. In adults these changes probably reflect an increase in ventilation/perfusion disturbance secondary to pulmonary vasodilatation. There were certainly cardiovascular effects in our infants, shown by tachycardia. Ventilation/perfusion disturbances may be more likely to occur in infants, because babies do not have any of the ameliorating effects of bronchodilatation in response to salbutamol, in spite of the fact that they do have functional airway β-adrenoceptors.[14] Airway obstruction may actually increase after bronchodilation, contributing to hypoxaemia.[4]

Jet nebulisation causes a gradual increase in the osmolality of the nebulisate. This is more likely to occur with long nebulisation times and small starting volumes,[15] and occurs with both the nebulised saline and with salbutamol.[15 16] This increase in osmolality could explain the adverse effects on airway function in wheezy infants, although these effects seem to be short lived.[17]

In contrast both the hypoxic effects of salbutamol and the decline in forced expiratory flow rates were still present 20 minutes after nebulisation, suggesting a persistent pharmacological effect.[4]

The validity of our results may be questioned because these infants were studied while asleep under sedation with chloral hydrate. Although oxygen consumption and production of carbon dioxide have been shown to be slightly higher in infants under sedation with chloral hydrate, this type of sedation produces steady oxygen consumption, endogenous carbon dioxide production, and end tidal $PCO_2$, and does not affect carbon dioxide chemoreceptor responsiveness, thus providing stable baseline readings from which to calculate changes in oxygen and carbon dioxide concentrations.[18] Face mask application causes changes in respiratory patterns in infancy.[19] All recordings of $SaO_2$, $PtcO_2$, and $PtcCO_2$ were taken after removal of the face mask, allowing for a period of stabilisation

Transcutaneous measurements provide indirect values for $PaO_2$ and $PaCO_2$, but these values do bear a close and proportional correlation with the true values.[20–23] Changes in transcutaneous values should therefore indicate arterial changes as long as the coefficient of proportionality remains unchanged. We cannot be sure that nebulised salbutamol did not change cutaneous blood flow, but the relative stability of $PCO_2$ readings argues against this. In addition, the parallel decline in $SaO_2$ and $PtcO_2$ reinforces the validity of the transcutaneous measurements.

This study has important clinical implications. As well as showing a paradoxical effect on airway function in wheezy infants,[4] we have shown that nebulised bronchodilators may have an adverse effect on arterial oxygenation. The effect persisted for at least 20 minutes It may be that in the presence of more severe airway obstruction and hypoxaemia a more severe adverse reaction to nebulised bronchodilator could occur: this would require urgent treatment with oxygen.

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# Nocturnal cough in asthma

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SUMMARY The timing of nocturnal cough and its association with change in ambient temperature was documented in 11 asthmatic children, median age 5·1 years, while they were receiving continuous prophylaxis. Studies were performed in their homes on three nights. A voice activated system with electronic time signal recorded coughing. Ambient temperature was recorded every five minutes throughout the night on a Grant Squirrel data logger. Ten children coughed on 27 nights with a median of six bouts of coughing a night (range 0–272). The cough rate in the two hours after going to bed was significantly higher than the cough rate in the middle of the night (2–4 am or 4–6 am). Peak coughing times were 7–9 pm and 6–8 am. The room temperature was lowest between 5 and 7 am. There were no significant differences between cough rates during periods of rapid temperature change (more than 1°C an hour). The timing of nocturnal cough observed in this study differed from the known basophase of circadian cycles described for adults and children.

Coughing is a common nocturnal symptom in children with asthma that has received little attention even in laboratory based studies.[1 2] Its association with other symptoms of nocturnal asthma and with circadian changes in lung function is unknown. There is evidence that symptoms are worst when peak expiratory flow rates are lowest, usually between 2 and 5 am,[3] but there is no published information, to our knowledge, on the precise timing of cough. We therefore documented the timing of cough during the night in asthmatic children on maintenance prophylaxis for asthma. We also recorded ambient temperature trends in the bedrooms of these children, as such data are not currently available.

## Patients and methods

Eleven patients attending the paediatric respiratory clinic at this hospital with moderate to severe asthma and night time coughing were invited to participate in the study. In seven the daytime control of asthmatic symptoms was good; daytime and nocturnal symptoms were present in the remaining four. Their median age was 5·1 years (range 2·7 to 10·5) and only two were over 6 years Five children were taking regular inhaled or oral steroids, two sodium chromoglycate, and three the theophylline preparation, Slo-Phyllin. All were taking regular selective $\beta_2$-agonists. In each case the last dose of medication was taken at bedtime.

The studies were performed in the patients' homes on three (usually consecutive) nights. No attempt was made to change the child's normal bedtime environment. No child slept with feather pillows or quilts, and there were no pets in the bedrooms. We did not measure housedust mite population or the humidity of the room. Equipment was set up and checked each night The system for recording coughing was based on previously described cough recorder systems.[4 5] A directional microphone was placed near the bed. A voice activated switch started a UHER 4200 tape recorder at noise above a threshold level which had been set individually for each child. An acoustic delay link ensured that the recorder was at operating speed by the time the triggering noise reached the tape recorder. After the noise stopped an electronic time signal was automatically recorded on a second channel of the tape recorder and the tape stopped. The tape was checked each morning to ensure that data had been recorded. One tape usually held three nights' recordings. The tapes were analysed simultaneously aurally and through a BBC computer which 'listened' to the tape in 10 second epochs. For each epoch of noise, the operator could record whether the data were due to coughing. The time of that epoch was then decoded, displayed, and stored.

Ambient temperature was recorded and stored using a Grant Squirrel data logger SQ32.2U 2U programmed to take readings at preset intervals of five minutes throughout the night The probe recorded temperatures within the range −5 to +45°C and was calibrated against a mercury and glass thermometer of resolution 0·1°C. The data were retrieved through a BBC computer which gave full lists of data and trend graphs. The results were analysed by the Wilcoxon matched pair signed rank tests

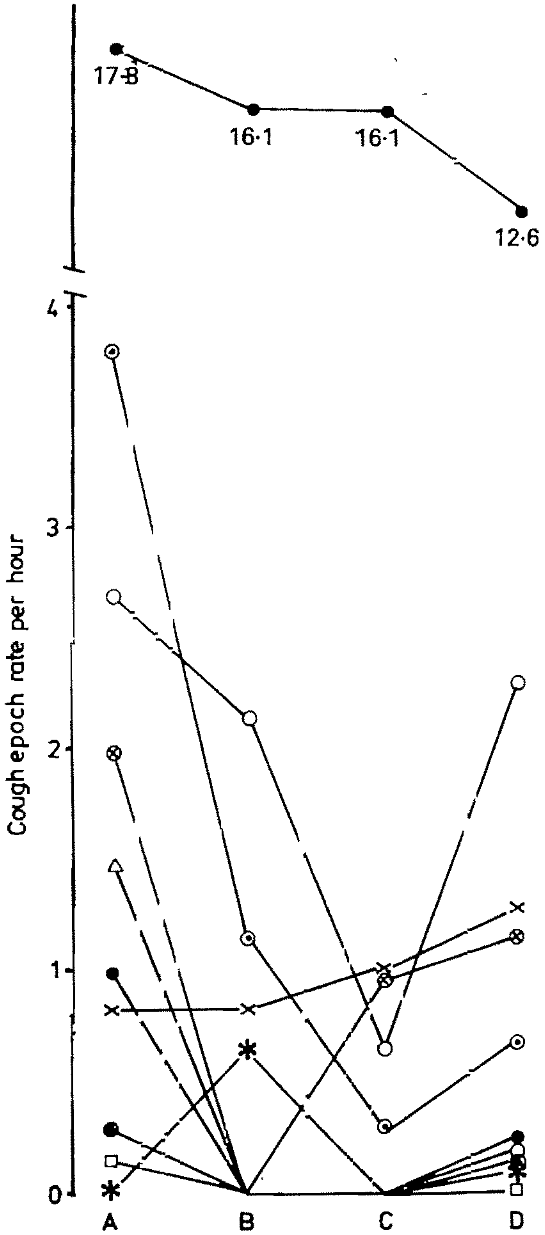

Fig 1 *Cough epoch rate/hour for individual cases during four two hour time periods (A=two hours after going to bed, B=2–4 am, C=4–6 am; D=two hours before rising )*

## Results

Eleven children were studied on 33 nights. One child did not cough at all. The remaining 10 children coughed on 27 nights with a median of six epochs (range 0–272) of coughing per night. Scrutiny of individual results showed a pattern in which most coughing occurred shortly after going to bed and before rising. We therefore arbitrarily divided the night into three periods: two hours after going to bed; two hours before rising; and the remainder of the night. The cough epoch rate per hour in the two hours after going to bed was significantly higher than during the rest of the night ($p<0\cdot05$) but no different from the two hours before rising. Fig 1 shows that the rate in the two hours after going to bed was also significantly higher than the rate during the time periods 2–4 am ($p<0\cdot05$) and 4–6 am ($p<0\cdot05$). The increase in the rate of coughing in the two hours before rising was not significant.

The data were then examined in real time. The children went to bed and rose at different times, giving a coughing pattern throughout the night. When the number of nights during which coughing occurred was expressed as the percentage of the nights that children were in bed at that time—that is allowing for different bedtimes—two peaks emerge—from 7–9 pm and 6–8 am (fig 2). Although there was variation in coughing times from night to night for individual children, five coughed predominantly in the first half of the night; one in the second half, and four intermittently throughout.

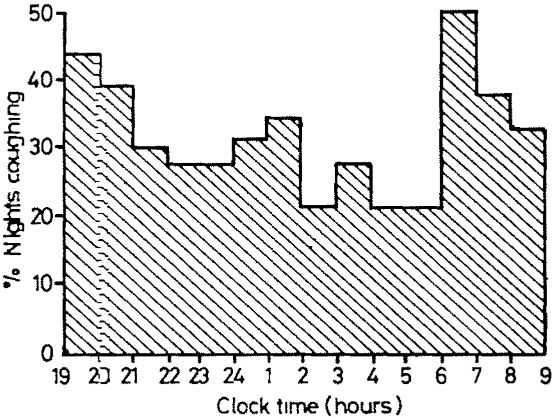

Fig 2 *No of nights when coughing occurred expressed as % of no of nights during which observations were made at any particular hour.*

The children took their regular drugs during the study. With two exceptions these were given within 90 minutes of bedtime (the exceptions were at our request early in the study and on both occasions the children required drugs during the night). On 11 nights coughing occurred within two hours of the regular drugs being given; on 18 nights within four hours; on 21 within six hours, and on 22 within eight hours. Two children used additional drugs during the night (four nights). This coincided with the end of a period of coughing that recurred after a mean of 64 minutes.

The mean (SD) ambient room temperature was 18·4°C (1·95) (range 14·4–21·8). The minimum temperatures usually occurred between 5 and 7 am. We calculated the change in temperature during each hour. There were no differences between cough epochs occurring when there was a change in temperature of greater than 1·0°C in an hour and in those when the temperature change was less than 1·0°C in an hour when paired comparisons were made for each child.

## Discussion

Parental recording of nocturnal cough scores has been shown to be a poor reflection of actual events.[4] All recordings were made in children whose parents had reported troublesome night time coughing, yet the median number of cough epochs per night was only six. Part of the explanation for this apparent disparity may lie in the timing of night time cough shown by this study. The parents may have been most aware of their children's coughing in the hours before they themselves retired and again in the hours before rising.

The timing of cough was an unexpected finding in our study. Although there are no directly comparable data on coughing, nocturnal events have been studied in children with asthma. Kales recorded wakenings with asthmatic symptoms in a temperature controlled (<20°C) sleep laboratory in 10 children on 20 nights.[1] The events were not reported in real time but no awakenings occurred in the first four hours after sleep had started and they were then evenly distributed throughout the remainder of the night, with few events occurring in deep sleep (stages 3 and 4). Smith and Hudgel showed a fall in forced expiratory volume in one second when asthmatic children were wakened at 3 am compared with values at 9 pm and 6 am, and maximum falls in oxygen saturation were greater from 2am–3 am than in the first hour of sleep.[2]

Maximum respiratory flows derived from flow volume loops were greater at 5–6 pm than 8–9 am,[6] and a significant rhythm in peak flow recordings was found in 14 of 64 children with symptoms of asthma with a bathyphase from 11 pm–4 pm.[7] Circadian rhythms have also been shown in the airway resistance of normal children with acrophase 3.30–5.30 am.[8] These findings suggest that children are most vulnerable to asthmatic attacks in the middle of the night. Surprisingly, the frequency of coughing was greater at the beginning and end of each night. In the studies quoted above coughing was not recorded as a separate variable, and its exact association with other signs and symptoms of nocturnal asthma remains unknown.

Several explanations are possible. The children we studied were younger than those in previous studies. Children under 6 can seldom perform conventional lung function tests, which explains the absence of data on circadian events in this age group. Coughing at night may be influenced by factors other than bronchial reactivity; and part of the explanation may lie in the sleep pattern. The influence of sleep stage on coughing in asthmatic children is unknown, but in adults with chest disease coughing is most common when awake and least common during deep sleep.[5] In home based studies it is not possible to define sleep stage or to determine exactly when children fall asleep. It is possible that early coughing occurred when the children were awake, but unlikely that they took up to two hours to fall asleep in their own environment; even in a sleep laboratory children took only 24 minutes to fall asleep on the first night and seven minutes after settling on the third night.[1] There is also a decrease in mucociliary clearance during sleep in both normal subjects and in asthmatics, which may be relevant to the timing of coughing bouts throughout the night.[9]

Temperature was the only environmental factor studied which might have influenced coughing at night. Previous studies have found no association between respiratory symptoms reported by the parents and low temperature in the bedroom.[10 11] This study was not designed to determine the influence of ambient temperature on nocturnal coughing, but our observations suggest that changes occurring within the range measured did not influence the frequency of coughing. Controlled observations in a laboratory are therefore necessary.

The children studied were all moderate to severe asthmatics who were receiving continuous treatment. Even so, parents reported nocturnal coughing. Of the three most severely affected children, two had poorly controlled daytime symptoms and the third, whose daytime control was good, coughed mainly during the early part of the night. The timing of treatment did not greatly influence the timing of cough, which usually occurred within two hours of medication. The pattern of coughing on the five nights when theophylline was taken at bedtime did not differ significantly from that on other nights. On two occasions at the start of the study parents were instructed to omit the bronchodilator or theophylline, or both, at bedtime and each time treatment was required during the night. The pattern of coughing in individual children did not change on nights when treatment was given at bedtime. Bronchodilators given during the night seemed to halt coughing spells, but the effects were temporary. The timing of symptoms shown by this study, with peaks of coughing some 12 hours apart, lends support to the idea that improving 24 hour asthmatic control will minimise nocturnal symptoms.[12]

We thank Mr G Sargent and Mr F Goodenough for technical help. Allen and Hanbury provided financial support

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# Reduced incidence of tuberculosis by prophylactic chemotherapy in subjects showing strong reactions to tuberculin testing

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SUMMARY The introduction of chemoprophylaxis with rifampicin and isoniazid in 1981 significantly reduced the incidence of tuberculosis. Between 1978 and 1981 children accounted for 136 of 642 notified cases, and this was reduced to 55 of 418 between 1982 and 1986. This effect was most obvious among children from the Indian subcontinent who comprised 80·2% of the children treated. The incidence among white children was not affected. Few side effects occurred and only two of 339 (0·6%) later developed clinical tuberculosis. Chemoprophylaxis plays an important part in the management of tuberculosis in a district with a high incidence of the disease.

The Blackburn local government area had the highest incidence of tuberculosis in England and Wales in 1970,[1] the fourth highest between 1978 and 1979,[2] and the fifth highest in 1983.[3] Immigrants from the Indian subcontinent accounted for 70 to 80% of notifications for these years. Nearly 20% of all notifications in the health district for 1978–80 were of children 0 to 15 years old, 89% of them being from the Indian subcontinent despite an active neonatal vaccination programme with Bacillus Calmette Guerin (BCG), with a 92% average acceptance rate. In 1981 the paediatric notifications rose to 55 of 164 (33·5%) of all notifications (table 1).

Because of the continuing high incidence of tuberculosis in the general population, and in children in particular, routine prophylactic chemotherapy was introduced in November 1981 throughout the district. Secondary chemoprophylaxis—that is, after evidence of exposure—was not used routinely before 1981, although primary chemoprophylaxis with isoniazid 5 mg/kg was given to the babies of women diagnosed as having sputum smear or culture positive pulmonary tuberculosis in the last trimester of pregnancy until active immunisation with isoniazid resistant BCG was effective.

Table 1 *Notifications of cases of tuberculosis 1978–81*

| | *1978* | *1979* | *1980* | *1981* |
|---|---|---|---|---|
| Total No of notifications | 130* | 186* | 162* | 164 |
| No of children from Indian subcontinent | 14 | 29 | 29 | 37 |
| No of white children | 4 | 3 | 2 | 18 |
| Total No of children | 18 | 32 | 31 | 55 |
| Total No of children as % of total No of notifications | 13 8 | 17 2 | 19 1 | 33 5 |

*Figures underestimate due to undernotification

The Joint Tuberculosis Committee of the British Thoracic and Tuberculosis Association suggested giving isoniazid 5 mg/kg alone, or with additional ethambutol 15 mg/kg, to children whose skin tests were positive for tuberculin.[4] The evidence in favour of using isoniazid alone comes from several studies of contacts,[5–7] and of patients with fibrotic, inactive lesions.[8] The usual regimens of isoniazid were 5 mg/kg for 26–52 weeks, 52 weeks being more effective than 26 weeks for inactive pulmonary lesions.[8] Isoniazid has few side effects and some of those reported may be attributed to the sporadic occurrence of hepatitis in the community. Thompson reported hepatitis in 0·5% receiving the drug and in 0·1% taking placebo.[8] In the United States Public Health Service trials in contacts isoniazid was stopped because of side effects in 1·9%, compared with 1·5% for those taking placebo alone[9] Brunner also showed that the incidence of hepatitis in patients taking isoniazid was rare.[10] Some authors[11] have considered the risk of emergence of organisms resistant to isoniazid to be unfounded, but Gryzbowski *et al*[6] showed that of those given isoniazid chemoprophylaxis who subsequently developed active disease, 16% had organisms resistant to the drug. They were, however, unable to show whether this resistance had been present initially or whether it was due to treatment with the single drug alone.

The regimen chosen initially was isoniazid 10 mg/kg and rifampicin 10 mg/kg, with pyridoxine 10 mg daily for nine months. Rifampicin was included to reduce the length of treatment, and because of the high incidence (6%) locally of primary isoniazid resistance seen in the index cases from the Indian subcontinent.[12] The dosage of rifampicin (10 mg/kg) was chosen because this was at the lower end of the dose range of 10–20 mg/kg recommended for children, and older children of 30 kg and over would not receive a dose above the maximum recommended of 600 mg/day. Because of the high incidence of the disease in children in 1981 when the regimen was introduced, the duration of the initial course was deliberately made longer than we intended to use later (six months), to make as large an impact as possible on the incidence in children.

## Methods

A district contact clinic was set up in November 1981 and held weekly. All contacts of index cases of tuberculosis, children who showed a positive reaction to tuberculin skin testing at school, and all new immigrants were referred for *x*-ray picture, physical examination, and tuberculin test (Tine) reading. The criteria set out for chemoprophylaxis in 1981 at the beginning of the scheme have remained the same. Chemoprophylaxis was advised in children from 0 to 15 years if they had a positive tuberculin test of grade 2, 3, or 4 with no history of BCG vaccination; a positive tuberculin test grade of 3 or 4 with a history of BCG vaccination, had recently become positive to a tuberculin test; or if they were new immigrants with grade 3 or 4 positive tuberculin tests, or had a 'healed' lesion shown on *x*-ray picture.

These criteria are similar to those subsequently recommended by the Joint Tuberculosis Committee in 1983,[13] and in an editorial in the *Lancet*[14] on prevention of tuberculosis with isoniazid. The Joint Tuberculosis Committee recommended isoniazid 10 mg/kg for six to 12 months.

After initial assessment by the chest physician children who fulfilled the above criteria were recommended to have chemoprophylaxis. From November 1981 to December 1983 inclusive a nine month regimen of isoniazid 10 mg/kg, rifampicin 10 mg/kg, and pyridoxine 10 mg, all taken once daily, was given. From January 1984 to December 1986 a six month regimen with identical doses was given.

Compliance was monitored by monthly visits from the health visitor who also checked with the chemists and general practitioners that regular prescriptions were being obtained. Children were seen every three months at the clinic during the course of treatment and had an *x*-ray picture taken before chemoprophylaxis was stopped. From November 1981 to December 1984 children were checked six and 15 months after drug treatment was stopped. From January 1985 children were discharged after completing the six months' course.

The case notes of all children notified as having tuberculosis between 1978 and 1980 were reviewed. These cases were true notifications with evidence of primary tuberculosis or mediastinal tuberculous lymphadenopathy on chest *x*-ray picture, or histological evidence of non-pulmonary tuberculosis. No child had been notified for chemoprophylaxis rather than treatment. There has been no change in the consultant staff in chest medicine or paediatrics since 1981, and they have maintained the same clinical criteria for the diagnosis of tuberculosis throughout.

## Results

Table 2 shows the number of children given chemoprophylaxis, the duration of treatment, and the ethnic distribution. Drug reactions were uncommon. Four children of 339 (1·2%) had their chemoprophylaxis changed to isoniazid 10 mg/kg and ethambutol 15 mg/kg because of vomiting. No case of rash, obvious liver function abnormality, or peripheral neuropathy was seen. Only two children of 339 (0·6%) who received chemoprophylaxis subsequently developed clinical tuberculosis (one each in 1985 and 1986), and there were reservations about compliance in these cases. Four children whose parents refused to give them chemoprophylaxis when so advised developed clinical tuberculosis within 12 months of that advice.

Table 3 shows notifications for 1978 to 1986. There are significant differences between the total

Table 2 *Details of chemotherapy regimens*

| *Year of study* | *Duration of treatment regimen (months)* | *No of patients* |
|---|---|---|
| November 1981–December 1982 | 9 | 118* |
| 1983 | 9 | 102* |
| 1984 | 6 | 43* |
| 1985 | 6 | 31 |
| 1986 | 6 | 45 |

*Followed up for 15 months after treatment.

Table 3 *Notifications of children with tuberculosis 1978–1986*

| | *1978* | *1979* | *1980* | *1981* | *1982* | *1983* | *1984* | *1985* | *1986* |
|---|---|---|---|---|---|---|---|---|---|
| No of children notified (Indian subcontinent) | 14 | 29 | 29 | 37 | 20 | 7 | 4 | 6 | 2 |
| % Of total notifications (Indian subcontinent) | 17·1 | 22·5 | 23·6 | 36·6 | 27·4 | 11·1 | 10·5 | 14·6 | 4·1 |
| No of children notified (white) | 4 | 3 | 2 | 18 | 4 | 5 | 6 | 0 | 1 |
| % Of total notifications (white) | 8·3 | 5·3 | 5·1 | 28·6 | 12·1 | 15·2 | 17·6 | 0 | 3·6 |
| Total No of children notified | 18 | 32 | 31 | 55 | 24 | 12 | 10 | 6 | 3 |
| % Of total No of cases notified | 13·8 | 17·2 | 19·1 | 33·5 | 22·6 | 12·5 | 13·9 | 9·0 | 3·9 |

notifications from 1978 to 1981 compared with those for 1982–86 ($\chi^2=11{\cdot}04$, $p<0{\cdot}001$) and those from 1978–81 compared with those from 1984–86 ($\chi^2=16{\cdot}75$, $p<0{\cdot}001$). Differences in notifications of cases of tuberculosis among children from the Indian subcontinent are also significant when the same time periods are compared ($\chi^2=10{\cdot}41$, $p<0{\cdot}01$, and $\chi^2=14.42$, $p<0{\cdot}001$, respectively). There were no significant differences in the number of notifications of white children.

## Discussion

There can be no doubt that the pattern of tuberculosis in the health district has been appreciably changed by the introduction of prophylactic chemotherapy. To allow for the considerable fall in notifications generally, the paediatric notifications were expressed as a percentage of their ethnic group and of the total for that year, to see if the ratio as well as the absolute numbers had fallen. It may be that the inclusion of the 1981 figures distorts the analysis because chemoprophylaxis was introduced during that year, but this was only in the last two months of the year and so was unlikely to have had any effect on the pattern of disease in that year. Furthermore, removal of the 1981 figures may have a negative bias on the results, as we know that the 1981 figures reflect the true pattern of disease, whereas the figures for 1978–80 are known to underestimate the incidence of the disease among children (table 1).

We thought that the introduction of chemoprophylaxis would have a much greater effect on the incidence of tuberculosis among children from the Indian subcontinent for the following reasons: (i) Immigrants formed 67·5% of the total and 89% of the paediatric cases in 1978–80 (table 1). (ii) A higher percentage of white index cases had pulmonary disease with positive sputum culture, so giving a higher incidence of clinical primary infection at first attendance, with less chance to intervene to prevent disease. (iii) In contacts from the Indian subcontinent group, a smaller percentage of those found subsequently to have clinical tuberculosis were found at the initial screening, so giving an increased chance of cure by chemoprophylaxis.[15] (iv) The estimated annual notification rate per 100 000 for the under 15 age group in the white ethnic group was 3·6, but for the Indian subcontinent group born in the United Kingdom it was 80/100 000 and for the Indian subcontinent group born abroad it was 183/100 000.[2]

The changed total pattern (table 3) is entirely due to the reduced incidence in tuberculosis in the children from the Indian subcontinent, there being no significant change in any year, or group of years, in the white ethnic group. This does not mean that chemoprophylaxis is not effective in the white ethnic group, but that no general population benefit can be inferred from the data.

It has been shown therefore, that the introduction of prophylactic chemotherapy in the group from the Indian subcontinent has benefited individual subjects and the general population. Because the incidence figures of tuberculosis in children given by the 1978/9 Medical Research Council survey[2] were annual, successful intervention with chemotherapy should have a cumulative effect: it should give benefit not just over the period of treatment, but also in subsequent years. In addition, as the number of children whose skin tests were strongly positive to tuberculin decreased over the period 1982–86 it implies that most of the reservoir of those at highest risk of developing tuberculosis had been given prophylactic treatment, which again has a cumulative effect on the pattern of the disease. The data in the group from the Indian subcontinent do show this trend, with no significant differences for the first year after the prophylaxis had started, but having an increasingly significant effect (with the exception of 1985 when two of the six cases were found on entry to the United Kingdom, and were thus not preventable by prophylaxis).

Although the Joint Tuberculosis Committee[13] recommended isoniazid 10 mg/kg for six to 12 months for prophylaxis, Horne, in an editorial discussing the Joint Tuberculosis Committee recommendations, noted that, 'studies to assess the efficacy of shorter regimens containing rifampicin are in hand'.[16] The six month regimen of rifampicin and isoniazid used from 1984–85 has also been used in some other areas with a high incidence of tuberculosis. It was successfully used in the Uppingham outbreak with no side effects reported.[17] Because of the success reported here and the low rate of relapse with a shorter duration of treatment, the duration of chemotherapy was reduced to a total of four months from 1 January 1987.

The criteria for chemoprophylaxis introduced from late 1981 locally conform to the recommendations of the Joint Tuberculosis Committee.[13] The introduction of chemoprophylaxis, although with a different drug regimen from that suggested by the Committee, has significantly reduced the incidence of tuberculosis in children from the Indian subcontinent. Chemoprophylaxis, therefore, has an important preventive role in the management of tuberculosis in areas with large immigrant populations. The combination of rifampicin and isoniazid may mean regimens lasting less than six months can be effective.

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# Psychological adjustment and diabetic control

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SUMMARY Glycosylated haemoglobin concentrations, C peptide secretion, insulin dose, psychiatric state, intellectual functioning, and the extent to which the implementation of the diabetic regimen was shared between parent and child were studied in a cross sectional study of 50 children with diabetes aged 6–16. Indications of psychological disturbance in the children and their parents predicted low glycosylated haemoglobin concentrations in the children, and accounted for 44% of variance in blood glucose control. The child's early and independent participation in the implementation of the diabetic regimen was associated with poor control.

Children and adolescents with insulin dependent diabetes mellitus who have problems in maintaining blood glucose control often have emotional disturbance as well.[1 2] Where problems in blood glucose control have not been severe enough to warrant recurrent admissions to hospital, the evidence for an association with psychological disturbance has been less consistent.[3–7] The inconsistencies may be due to measures of blood glucose control which are open to bias and error, failure to consider biochemical indications of residual endogenous insulin secretion (C peptide), and superficial, unstandardised, single blind psychiatric evaluations. It is now possible to assay haemoglobin A1 ($HbA_1$) concentration, (which reflects average blood glucose concentrations over the past six to eight weeks), and standardised psychiatric assessment techniques have been developed that permit a more rigorous examination of the association between psychological adjustment and diabetic control.

The association between psychiatric disorder and poor blood glucose control has been explained by poor adherence to the diabetic regimen among psychiatrically disturbed patients.[8 9] We have examined the association between blood glucose control (measured by $HbA_1$ assay), psychological adjustment, and patterns of diabetic management in a sample of children for whom C peptide measurements and other clinical variables were available.

## Subjects and methods

The study comprised all 71 diabetic children (aged 6 to 16 years) attending the outpatient department of a rural district general hospital. Families of patients who met the selection criteria were approached individually. The criteria were duration of diabetes of at least six months, absence of major medical problems unrelated to diabetes, and absence of major intellectual impairment. Of the 61 patients meeting the criteria, 50 (85%) agreed to participate in response to a letter from the consultant.

Table 1 gives details of the children. There were slightly more over the age of 12, and the median duration of illness was 3·5 years. Social class was determined using the Registrar General's classification; the sample showed a slight bias towards middle class families. Fifteen per cent of the children came from broken homes. The 11 families who did not participate were comparable in sex ratio, social class, and age with the children studied, and 18% were single parent families.

The questionnaires were completed and psycholo-

Table 1 *Details of the 50 diabetic children studied*

| *Variable studied* | *Measurement* | | |
|---|---|---|---|
| | *Mean* | *(range)* | *No (%)* |
| Age (years) | 11·8 | (6·2–16) | |
| Duration of illness (years) | 4·2 | (0·8–12·7) | |
| $HbA_1$ concentration (%) | 11·9 | (7·6–18·1) | |
| Daily units of insulin/kg | 1·0 | (0·45–9·14) | |
| No of boys | | | 24 (48) |
| Children in social classes I and II | | | 16 (32) |
| One injection/day | | | 32 (64) |
| C peptide >50 pmol/l | | | 13 (26) |

gical assessments made when the parents and diabetic children made a special visit to their local clinic for the purpose of participating in the study. Single blood samples were obtained after breakfast within five days to 18 weeks (average five weeks) after collection of the psychological data. $HbA_1$ measurements were performed using the Corning electrophoretic method.[10] The normal reference range for the laboratory was 5–8%. Additional endocrine assays included measurement of C peptide secretion (blood glucose >8 mmol/l); plasma was considered to contain C peptide if the assay result was greater than 50 pmol/l (the detection limit of the assay). Clinical data recorded included units of insulin/kg and the percentage of children taking long acting insulin. Comparable data on endocrine function were not available for the children in the clinic who did not agree to participate in the study.

Intellectual and educational development were assessed using the Wechsler intelligence scale for children (revised) and the Schonell reading test. Information concerning psychological adjustment was collected using four independent sources. The parents completed a standardised questionnaire of psychological disturbance concerning their child, as did the child's school teacher.[12] The children received a standardised individual psychiatric assessment by semistructured interview with a consultant psychiatrist.[13] The interview offered children the opportunity to express themselves spontaneously on various topics or in play. The children also saw a psychologist for assessment and testing which included the Eysenck personality questionnaire (junior).[14] Neither examiner had information about the child's diabetic control. The parents' psychiatric states were assessed using the 30 item version of the general health questionnaire, a standardised self report.[15]

Information concerning the child's diabetic regimen was obtained using a specially derived 55 item questionnaire, the diabetic management profile, that was completed by the parents. This was divided into sections concerning diet, insulin injections, urine testing, blood testing, and a set of miscellaneous items relevant to the maintenance of diabetic control. Parents were asked to record the degree of responsibility taken by members of the family for specific parts of the child's diabetic management and to answer questions concerning emotional and behavioural aspects of the child's responses to the demands of the diabetic regimen. The questionnaire yielded scores on three sets of empirically devised scales covering the areas of adherence to the regimen, emotional response to the demands of treatment, and the degree of participation in implementing the regimen by the child and other members of the family. The agreement between mothers and fathers completing the questionnaire independently was 82%, and the mean alpha coefficient for the scales was 0·84.

Mean $HbA_1$ concentrations of the children, grouped according to parents' responses to items in the questionnaire concerning diabetic management, and according to the child's scores on the psychological tests used, were contrasted using two way analyses of covariance, with sex as the second grouping factor. Two sets of covariates were used. The first comprised the child's age and duration of diabetes; these ensured that differences between the groups could not be accounted for by age or duration of the disease. The second set of covariates extended the first by including C peptide secretion and daily dose of insulin (units/kg) to control for the effects of residual insulin production and insulin dose. Thus the procedure statistically equated the groups for variables known to be important determinants in control of blood glucose concentrations. In the case of continuous variables partial product-moment correlation coefficients were computed controlling for the same sets of variables. A multiple linear regression equation was computed using demographic, clinical, and psychiatric variables to identify the combination of biochemical indices, demographic characteristics, and measures of psychological disturbance providing the best prediction of $HbA_1$ concentrations.

## Results

Table 1 shows the clinical data and measurements of endocrine function. The mean $HbA_1$ concentration was high at 11·9%. Twenty six per cent of the sample had detectable C peptide in plasma indicating residual endogenous insulin secretion. The insulin dose (units/kg) correlated significantly with $HbA_1$ concentrations ($r=0{\cdot}28$, df=48, $p<0{\cdot}03$). C peptide secretion was not associated with $HbA_1$ concentrations. A separate analysis of the data on the subgroup of children over 12 years old, however, showed that the group with detectable C peptide had lower mean $HbA_1$ concentrations (12·2% and 10·4%, respectively), and this difference was significant ($F_1$, (df 21)=6·5, $p<0{\cdot}02$). In this age group the number of daily injections also predicted $HbA_1$ concentrations. Thirteen of 25 patients having two injections a day had a mean $HbA_1$ concentration of 11·4%, compared with 12·9% in those adolescent subjects having a single daily injection ($F_1$, (df 21)=5·8, $p<0{\cdot}04$). Cognitive functioning did not predict $HbA_1$ concentration.

As children behave differently under different circumstances, multiple screening was used to avoid missing genuine cases of psychological disorder.[16] Psychosocial adjustment was assessed in terms of the persistence and severity of emotional and behavioural problems, using three psychometric tests and an interview with the child by a psychiatrist. The recommended cut off scores were used for all tests to identify children with appreciable emotional and behavioural difficulties.[12] [13] About 25% of children showed some indication of disturbance in at least one of the tests used, and 6% of the children showed signs of severe psychiatric disorder according to the psychiatrist's rating. The extent of overlap between the screening tests for parents and teachers was low (45%), but the agreement of these with the psychiatric rating was higher (55% for teachers and 78% for parents).

There was a consistent association between good control of blood glucose and psychiatric disturbance using several measurements. A strong negative correlation emerged between $HbA_1$ concentrations and the neuroticism scale of the Eysenck personality questionnaire ($r=0{\cdot}49$, $df=44$, $p<0{\cdot}001$). Neuroticism scores were higher for children with moderately better glycaemic control, but no further associations with glycaemic control were observed on the other variables in the Eysenck personality questionnaire (table 2). Among younger children (under 12 years), those noted to have psychological problems (by parents, teachers, or the psychiatrist) had significantly lower $HbA_1$ concentrations than those in whom disturbance was not found (table 2). Analyses of covariance showed that these associations could not be accounted for by differences of insulin dose or C peptide secretion. Analysis of the single items of the screening tests showed that a larger number of specific symptoms of emotional disturbance predicted low $HbA_1$ concentrations better than did specific symptoms of behavioural disturbance. Examples of the symptoms of emotional and behavioural disturbance which predicted $HbA_1$ values included worry—as noted by the parents ($F_1$. (df 38)$=4{\cdot}6$, $p<0{\cdot}04$)—apprehension—as noted by the teacher at school ($F_1$, (df 41)$=6{\cdot}2$, $p<0{\cdot}01$)—and a tendency to bully other children—as noted by the parents ($F_1$, (df 33)$=6{\cdot}2$, $p<0{\cdot}02$). Thus several psychiatric measurements showed that children with psychological difficulties had significantly better blood glucose control than those in whom there were no problems of psychological adjustment.

The association between parents' psychological disturbance and their child's metabolic control was similar. Children whose fathers were classified as probable psychiatric cases by the screening tests were found to have better blood glucose control

Table 2 *Mean $HbA_1$ concentrations of children with and without behavioural and emotional problems*

| | *No of cases* | *Mean $HbA_1$ (SE) (%)* | *Statistics* |
|---|---|---|---|
| *Total sample.* | | | |
| Problems noted at home (symptom score >13) | 9 | 11·1 (0·4) | |
| No psychological disorder noted (symptom score <13) | 36 | 12·6 (0·5) | $F_1$ (df 36)=7·0, p<0·02† |
| Self-rated neuroticism (mean=9·7, SD=4·8). | | | |
| Low (1–5) | 12 | 13·7 (0·6) | |
| Moderate (6–14) | 23 | 11·9 (0·3) | $F_2$ (df 38)=8·6, p<0·001* |
| High (15–18) | 6 | 10·9 (0·6) | $F_2$ (df 29)=3·9, p<0·03† |
| *Children under 12* | | | |
| Problems noted by psychiatrist, parent, or school | 14 | 11·1 (0·4) | $F_1$, (df 18)=9·6, p<0·006* |
| No psychological disorder noted | 8 | 13·4 (0·7) | $F_1$, (df 16)=5·4, p<0·04† |

*Results of the analysis of covariance controlling for age and duration of diabetes
†Results of the analysis of covariance controlling for age, duration of diabetes, C peptide, and daily units of insulin/kg

Table 3 *Mean $HbA_1$ concentrations of children grouped according to parents' psychiatric problems*

| | *No of cases* | *Mean $HbA_1$ (SE) (%)* | *Statistics* |
|---|---|---|---|
| *Mother:* | | | |
| Probable case (score >4) | 12 | 11·3 (0·5) | |
| Not probable case | 33 | 12·3 (0·3) | $F_1$ (df 34)=5·3, p<0·03† |
| *Father* | | | |
| Probable case (score >4) | 8 | 10·1 (0·7) | $F_1$ (df 33)=7·9, p<0·008* |
| Not probable case | 29 | 12·2 (0·6) | $F_1$ (df 27)=5·7, p<0·03† |

*Results of the analysis of covariance controlling for age and duration of diabetes
†Results of the analysis of covariance controlling for age, duration of diabetes, C peptide, and daily units of insulin/kg

(table 3). Similarly, children whose mothers scored in the pathological range had significantly lower $HbA_1$ concentrations than children whose mothers' score did not place them in the disturbed group (table 3).

Only one of the three sets of scales of the diabetic management profile was found to predict $HbA_1$ concentrations. The scale measuring the child's independence in implementing various aspects of the treatment regimen was found to correlate with poor blood glucose control when age and duration of illness were checked ($r=0{\cdot}30$, df=47, $p<0{\cdot}01$). Those children under the age of 12 who relied on their parents for help in implementing various aspects of the regimen were particularly likely to have lower $HbA_1$ concentrations ($r=0{\cdot}61$, df=17, $p<0{\cdot}002$). A number of individual items which made up this scale predicted $HbA_1$ concentrations; children who independently administered their injections ($F_{2,}$ (df 38)=3 1, $p<0{\cdot}05$) and tests for glycosuria ($F_{1,}$ (df 35)=4·1, $p<0{\cdot}02$) and who were responsible for the timing of their meals ($F_{1,}$ (df 36)=3·2, $p<0{\cdot}05$) had higher $HbA_1$ concentrations, even when the influence of age and duration of disease was allowed for.

The association between the child's independence in management and $HbA_1$ concentrations accounted for some of the common variability between psychological disturbance in the children and blood glucose control. For example, the correlation between the presence of psychological disturbance rated by parents, teacher, or psychiatrist and $HbA_1$ concentration was 0·54 for the 22 children under 12 years. When the scale score for the child's independence in implementing the management was controlled for, however, the resulting partial correlation was substantially reduced ($r=-0{\cdot}09$, df=19, ns).

A hierarchical multiple linear regression was used to investigate the importance of the association of the measurements of psychological disturbance and glycaemic control. Initially all demographic and clinical variables were forced into the equation The backwards stepwise procedure eliminated all but residual endogenous insulin secretion in units of insulin/kg. A formal stepwise analysis was then used to specify the most important overall psychiatric measurements determining $HbA_1$ concentrations. Variables representing appreciable emotional and behavioural problems in the home, school, and psychiatric interview were considered, together with self rated neuroticism scores on the Eysenck personality questionnaire (junior). Two overall measures of psychological disturbance of the child (self rated neuroticism and the presence of appreciable psychological disturbance as perceived by the parents) were selected (table 4). A further stepwise procedure was then used to see if specific emotional and behavioural symptoms identified by the parents, teachers, and the psychiatrist could add to the prediction of $HbA_1$ concentrations made by clinical and overall psychiatric measurements. One such measurement, the restlessness of the child during the psychiatric interview, added slightly to the predictive power of the equation. Thus three psychiatric variables were selected and these combined with the clinical variables accounted for 44% of the variance in $HbA_1$ concentrations (table 4).

Table 4 *Results of the multiple linear regression: psychiatric predictors of diabetic control*

| *Variables* | *Weights* | *t statistic* | *p values* |
|---|---|---|---|
| C peptide | −0·58 | −1 72 | 0·09 |
| Units of insulin/kg | −1·31 | −2 46 | 0·02 |
| Neuroticism | −0·20 | −3·66 | 0·007 |
| Psychological problems noted at home | −2 00 | −2 94 | 0·006 |
| Gross activity level in psychiatric interview | −1·95 | −2·53 | 0·02 |

R=0 66, $F_5$ (df 42)=6 48, p<0 0002

## Discussion

The findings suggest that between a quarter and a third of children with insulin dependent diabetes mellitus have appreciable emotional and behavioural problems. This is higher than may be expected in a rural sample. In the absence of more rigorous methods of sampling the comparison between the present study and larger scale epidemiological surveys is not possible. The prevalence observed is, however, similar to that reported in other studies using an overlapping set of tests.[5 7]

There was a moderately strong association between indications of psychiatric disturbance in diabetic children and their parents, and good control of blood glucose. The strength and reliability of these associations using a number of measures are remarkable because they contrast with those found in past investigations with perhaps less comprehensively evaluated samples.[5 17] Several authors have reported that chronic poor control associated with frequent hospital admission (brittle diabetes) is likely to be the consequence of major psychological difficulties.[1 18 19] The present findings indicate that while patients with poor control may often be psychiatrically disturbed, psychiatric disturbance per se is not inevitably a cause of poor control in children. Indeed, it may be that anxious children tend to be more diligent in monitoring the subjective signs of poor blood glucose control and they counteract these more effectively.

The results indicate that the child's assumption of responsibility for the administration of the regimen is associated with poor blood glucose control in children under the age of 12. Observational studies examining the quality of self management among children of this age have shown that both knowledge[20 21] and skills in managing diabetes[20] are generally less than adequate. Parental participation in implementing the regimen may well ensure the provision of resources which are necessary but not sufficient to ensure good glycaemic control.[22] These findings suggest a need for further research concerning the desirability of starting self care early in children with diabetes.

Psychiatric measurements predict $HbA_1$ concentrations independently of C peptide secretion. Parents who see themselves as taking a greater role in helping to administer the treatment were more likely to have children with reasonably good glycaemic control but with appreciable behavioural and emotional problems. When parental perceptions of the child's independence in management were analysed statistically, the association between glycaemic control and psychological disturbance was considerably reduced. We could thus interpret the data as indicating that anxious children may be more unwilling to take responsibility for the regimen, and their consequent dependence on their parents protects them from the adverse influence of precocious self care. In addition, anxious parents may be more concerned about their child's capacity to cope independently with the demands of the regimen and may therefore take a more active role in its implementation.

Our findings show a diversity of associations between psychological factors and glycaemic control, perhaps mediated by the range of coping responses of the children and their families that together make up the adjustment of the family to diabetes in the child

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# Blood spot glucocorticoid concentrations in ill preterm infants

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SUMMARY The adrenocortical response to stress was studied longitudinally in 10 ill preterm infants using measurements of cortisol and 17OH-progesterone concentrations in filter paper blood spots Mean cortisol and 17OH-progesterone concentrations reached a peak of 2200 nmol/l and 65 nmol/l, respectively, between the third and fifth days of life. These concentrations far exceeded those observed in older children and adults subjected to stress as a result of surgery. Further pulses of endogenous cortisol production of 4000 nmol/l or more occurred in association with clinical complications such as intraventricular haemorrhage. These results indicate that infants undergoing intensive care are unduly stressed. Consideration should be given to providing enough sedation and appropriate analgesia for ill preterm infants during painful procedures such as insertion of venous cannulae and arterial puncture

Increased plasma concentrations of 17OH-progesterone (17P) and cortisol in ill preterm infants have previously been reported.[1 2] These observations, which indicated a presumed stress response, were based only on single random measurements of plasma steroid concentrations. Little is known about the magnitude and duration of the adrenocortical response to stress in the newborn. A study of ill infants during the first three days after birth by Gutai *et al* showed that there was no significant increase in plasma cortisol concentrations. Most of the infants studied were not unduly stressed when assessed by clinical criteria[3] In a study of ill preterm infants with hyaline membrane disease,[4] however, the peak plasma glucocorticoid response achieved was related to the severity of respiratory distress.

Studies, in which serial measurements of plasma steroid concentrations in ill preterm infants have been made, have been limited by the difficulty of collecting venous samples from small infants. A steroid assay, which uses whole blood spotted on to filter paper, has recently been developed however,[5-7] and this technique, which requires only a small volume of blood, has been used to obtain longitudinal data on 17P and cortisol concentrations as an index of the adrenocortical response to stress in a group of ill preterm infants

## Patients and methods

Ten preterm patients were studied longitudinally for the first 13 days of life. All were very ill and required assisted ventilation for severe hyaline membrane disease. Table 1 presents their clinical details. Gestational age was assessed by the method of Ballard *et al.*[8] Arterial catheters (umbilical or radial) were inserted shortly after birth for measurements of blood gas and invasive blood pressure monitoring. When an arterial sample was collected additional drops were spotted on to a Guthrie card sufficient to fill completely four 10 mm circles. The date and time of each sample collection was recorded for each infant. The filter paper card was left to dry at room temperature before being sent to the laboratory for analysis. In five of the infants blood spots were obtained at about six hourly intervals for three to five days.

Blood spot 17P concentrations were determined by a specific radioimmunoassay.[7] A similar method was used to determine cortisol concentrations in blood spots, but solvent extraction was not required. Briefly, 50 μl of ethanol followed by 200 μl of phosphate buffer solution were added to each 6 mm disc punched out of a blood spot. $^{125}$I-labelled cortisol and an anticortisol serum that had been coupled to magnetisable cellulose were added to

Table 1 *Clinical details of 10 infants studied*

| *Case No* | *Sex* | *Birth weight (g)* | *Gestation (weeks)* | *Clinical problems* |
|---|---|---|---|---|
| 1 | F | 1860 | 32 | HMD, IVH, died at 14 days |
| 2 | F | 805 | 28 | HMD, PDA, died at 6 weeks |
| 3 | M | 1800 | 32 | HMD, IVH, NEC |
| 4 | M | 975 | 25 | HMD, IVH, PDA |
| 5 | M | 1850 | 30 | HMD, IVH, ARF |
| 6 | F | 1630 | 32 | HMD, PDA, ARF, pneumothorax |
| 7 | M | 780 | 25 | HMD, PDA, NEC, died at 22 days |
| 8 | M | 1140 | 31 | HMD, PDA, DIC, ARF |
| 9 | M | 850 | 25 | HMD, IVH, pneumothorax, died at 12 weeks |
| 10 | M | 1485 | 31 | HMD, IVH, ARF, died at 15 days |
| Mean | | 1313 | 28·8 | |
| Range | | 805–1860 | 24–32 | |

HMD=hyaline membrane disease, IVH=intraventricular haemorrhage, PDA=patent ductus arteriosus, NEC=necrotising enterocolitis, ARF=acute renal failure, DIC=disseminated intravascular coagulation

100 µl of the ethanol-buffer solution and the mixture incubated for one hour. Antibody bound and free steroids were separated using a magnetic tray and the radioactivity was counted in a multiwell gamma counter. Unknown sample concentrations were interpolated from the dose-response curve. Blood spot cortisol and 17P values were converted to the equivalent concentration in plasma based on the assumption that each disc contained 4·5 µl plasma.[7] For both assays the intra- and interassay coefficients of variation did not exceed 7·0% and 11·5%, respectively. Table 2 summarises the characteristics of the blood spot assays. Data were calculated as mean (SEM) and compared using Student's unpaired *t* test. In those infants from whom more than one sample was collected each day the mean steroid concentration was used to determine mean values for the total group of 10 infants studied.

## Results

Fig 1 shows the mean (SEM) blood spot cortisol concentrations determined serially in 10 infants from birth to 13 days of age. The mean cortisol concentration increased more than twofold during the first few days to reach a maximum of about 2000 nmol/l between days 3 to 5 Blood spot cortisol concentrations decreased during the ensuing four days, and thereafter stayed constant over the remainder of the study period. Fig 2 shows the

Table 2 *Relevant characteristics of blood spot radioimmunoassays*

| *Characteristic* | *Steroid* | | | |
|---|---|---|---|---|
| | *17OH-progesterone* | | *Cortisol* | |
| Sensitivity | 1·0 nmol/l | | 28 nmol/l | |
| Range | 1·0–550 nmol/l | | 28–2450 nmol/l | |
| Cross reactivity (%) | 17OH-pregnenolone | 7·4 | 11-deoxycortisol | 28 |
| | Progesterone | 5·9 | Cortisone | 23 |
| | 21-deoxycortisol | 1·5 | Corticosterone | 20 |
| | Pregnenolone | 0·3 | Prednisolone | 4·7 |

Cross reactivity=amount of steroid required to displace 50% binding of labelled 17P/cortisol at zero binding

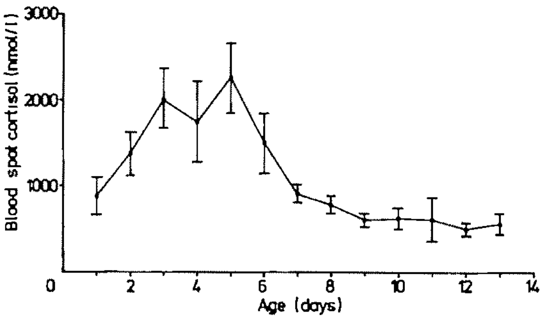

Fig 1 *Mean (SEM) blood spot cortisol concentration in ill preterm infants*

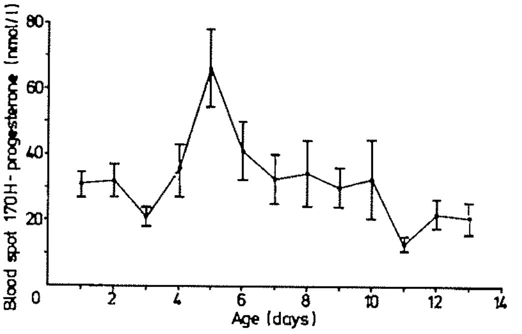

Fig 2 *Mean (SEM) blood spot 17OH-progesterone concentration in ill preterm infants*

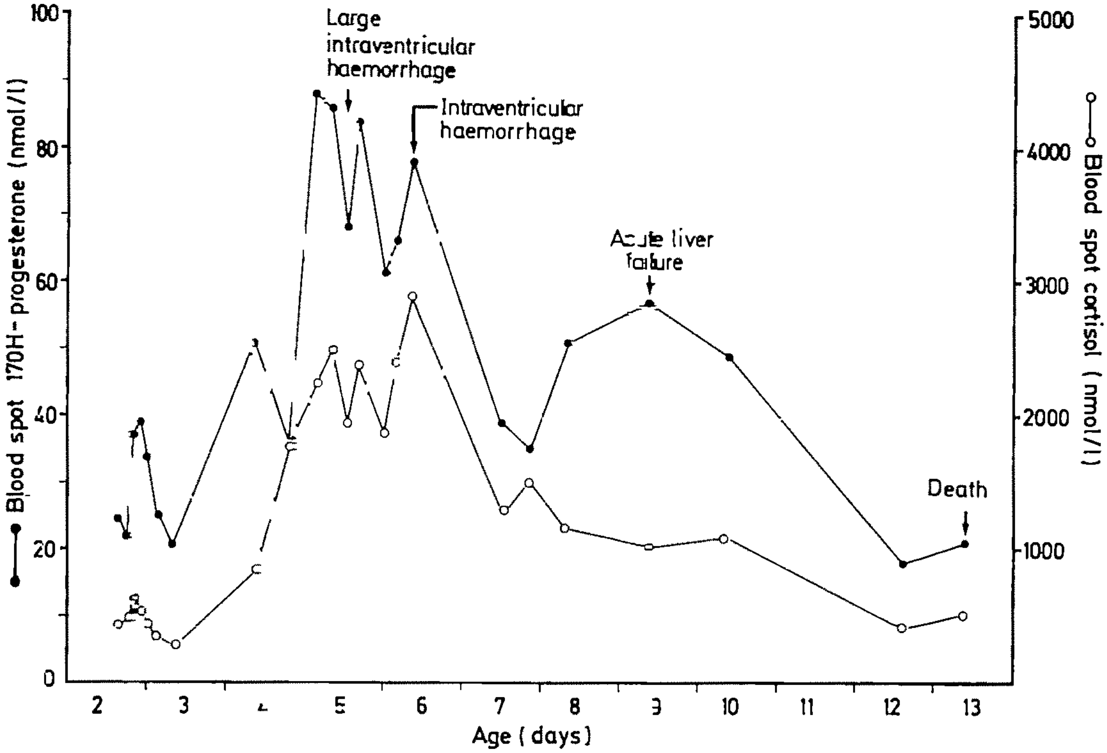

Fig 3 *Serial blood spot cortisol and 17OH-progesterone concentrations in an ill preterm infant: stressful clinical events (arrows).*

pattern of blood spot 17P concentrations measured over the same time period. Peak values were seen on day 5 with a mean 17P concentration of 65 nmol/l. The increased blood spot 17P concentrations in preterm ill infants compared with those measured in healthy full term infants (range 3–18 nmol/l) were still evident on day 13.

Fig 3 shows the individual blood spot 17P and cortisol concentrations in one infant who died. The peak cortisol concentration exceeded 4000 nmol/l; this coincided with the development of a large intraventricular haemorrhage shown on cranial ultrasonography. Extension of the blood into the brain parenchyma was accompanied by further pulses in cortisol secretion. The infant subsequently developed hepatic failure and died. Just before death the concentrations of cortisol fell. A similar pattern of secretion was seen in plasma 17P concentrations. Fig 4 shows the individual profiles of cortisol concentrations determined in serial blood spots collected from five infants. There was a large range of values, but most infants had cortisol concentrations consistently above 1000 nmol/l.

## Discussion

Mixed cord blood cortisol concentrations in healthy term infants are relatively high (800 nmol/l) but fall rapidly within 24 hours of birth to about 270 nmol/l.[9] The cortisol gradient may be the result of placental transfer of maternal plasma free cortisol, or it may be due to increased fetal adrenal activity because of the stress of delivery.[10] There is no obvious difference in cortisol concentrations between healthy term and preterm infants during the first 10 days after birth.[11]

The pattern of cortisol secretion in ill preterm infants seems to be quite different. In this study cord blood cortisol concentrations were not measured. Although individual cortisol concentrations varied widely during the first six days after birth, blood spot cortisol concentrations progressively increased reaching a peak on day 3. They remained constant for two days before decreasing gradually over the remaining eight days of the study. Even the smallest preterm infant seems to be able to secrete large amounts of adrenocortical hormones for a

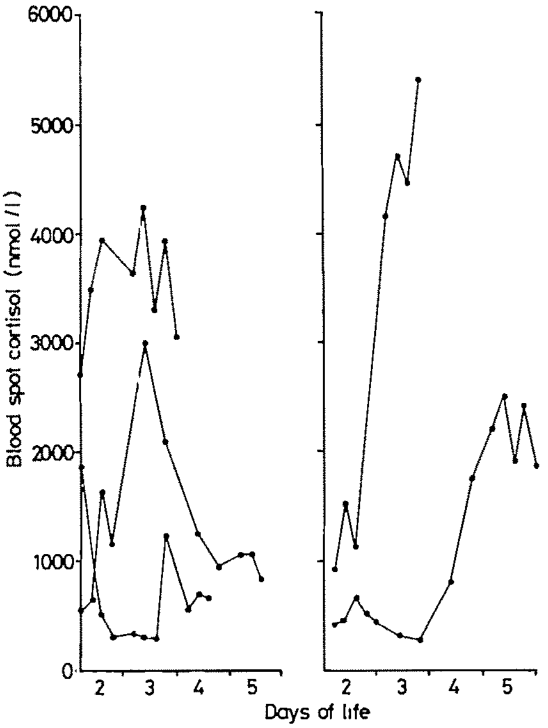

Fig 4 *Blood spot cortisol profiles in five ill preterm infants*

protracted period in response to stress. A similar response was observed in concentrations of 17P in response to stress. Interestingly, peak cortisol and 17P concentrations were delayed until days 3 and 5, respectively, even though the infants were generally most ill during the first 72 hours after birth.

Studies in newborn rats have shown that there is a clearly defined period when rats do not respond to stress.[12]: This is an interval immediately after birth during which the adrenocortical neonatal response to a variety of stresses is absent.[13] Corbier and Roffi[14] showed that in rats the period of absolute unresponsiveness to stress was followed by a period of relative unresponsiveness. The authors proposed that increased concentrations of corticosteroid, the principal glucocorticoid in rats, accumulate in the brain and inhibit the production of corticotrophin releasing factor. Alternatively, it was suggested that the absence of response was the result of a transient defect in adrenocorticosteroid synthesis. This is unlikely in view of the findings of a previous study which showed that ill preterm infants attain adequate concentrations of plasma cortisol if given adrenocorticotrophic hormone (ACTH).[2] If a similar period of absolute or relative unresponsiveness to stress also occurs in human neonates, this may be important in the early management of the very ill preterm infant.

The results of this study illustrate that small ill preterm infants experience considerable stress while undergoing intensive care Furthermore, an added clinical complication such as the extension of an intraventricular haemorrhage (fig 3) results in a further pulse of endogenous cortisol secretion. The pronounced changes in cortisol concentrations seen over 24 hours (fig 4) indicate that frequent sampling is required to define the period when a surge in adrenocortical activity occurs. Blood spot sampling is ideal for this purpose

Comparable studies in adults undergoing major and minor operations indicate that mean postoperative plasma cortisol concentrations reach 1080 nmol/l and 540 nmol/l, respectively,[15] values considerably lower than those achieved in ill preterm infants. The neonatal adrenal gland has a remarkable capacity for cortisol production; and Forest reported concentrations as high as 11 556 nmol/l in infants given ACTH 500 μg/m$^2$ twice daily for three days.[16] Newborn puppies subjected to haemorrhagic shock achieved cortisol concentrations up to 2000 nmol/l.[17] It was notable that the highest cortisol concentrations occurred in those puppies that died first. In a study of term infants undergoing cardiac operations with cardiopulmonary bypass, the plasma cortisol concentration increased from 356 nmol/l before operation to 781 nmol/l postoperatively.[18] When the stress response was reduced by the administration of analgesia, the infants were more stable postoperatively.

While the stress response may be beneficial in the short term there are some drawbacks. In the absence of hypovolaemia stress induces unwanted hypertension associated with the breakdown of protein and a negative nitrogen balance.[19] Transcutaneous oxygen measurements have shown that many core orientated stimuli given to preterm infants produce a fall in $pO_2$.[20] The results of the present study indicate that infants being given intensive medical treatment are even more stressed than those who have had surgery. Painful procedures liable to cause stress, such as insertion of venous cannulae and arterial stabs, perhaps should be accompanied by better sedation and the provision of appropriate analgesia for ill preterm infants.

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# Continuous four-channel EEG monitoring in the evaluation of echodense ultrasound lesions and cystic leucomalacia

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SUMMARY Continuous monitoring by electroencephalography (EEG) was performed in 31 preterm infants with echodense ultrasound lesions using the Oxford Medilog four channel recorder. In 12 infants these densities preceded cyst formation, eight in the periventricular and four in the subcortical region. In the 19 other infants the densities resolved.

The most severe EEG depression occurred in the four infants with subcortical cysts, who also had the poorest outcome. Six of eight infants with periventricular lesions had lesser degrees of abnormality though all infants had moderate to severe handicap at follow up. Similar abnormalities were seen on EEG recording in three infants in whom the densities resolved without cyst formation and these infants also had an abnormal outcome.

An abnormal EEG recording provides a sensitive early guide to the severity and prognosis of these lesions, even before they can be seen on ultrasonography.

Recent refinements in ultrasound techniques have permitted diagnosis of ischaemic as well as haemorrhagic lesions.[1 2] Ischaemic lesions initially present as areas of increased echodensity on ultrasonography; some resolve but others proceed to extensive cyst formation in the periventricular or subcortical white matter, referred to as periventricular or subcortical leucomalacia. The poor prognosis of infants with extensive cystic lesions has been well documented, but in those whose densities resolve the prognosis is more variable.[3-5]

Although prognosis based on the presence of extensive cysts seems to be reliable, the cysts are not present initially and may take two to four weeks to develop. Further aids to early prognosis would therefore be valuable. This study aimed to assess the prognostic value of early and sequential EEG recording in infants with echodense ultrasound lesions and subsequent extensive cystic leucomalacia.

## Method

Over 21 months 150 infants were entered into a prospective correlative study of EEG recordings and cranial ultrasonography. The 31 infants with persistent echodensities are reported here. Their mean gestation was 31 weeks (range 27–36) and mean birth weight 1230 g (range 720–2150).

### ULTRASOUND ASSESSMENT

Ultrasound assessment was made daily during the first week of life and then twice weekly, using an ATL Mark 3 sector scanner (3·5–7·5 MHz crystal). Densities were defined as unilateral or bilateral areas of increased echogenicity seen in both coronal and parasagittal views that persisted for at least 48 hours. Their evolution was classified as resolution without cyst formation, or extensive cyst formation in the periventricular or subcortical white matter.

### EEG ASSESSMENT

An Oxford Medilog 4–24 continuous four channel monitor was used.[6] Electrocardiogram, respiration, and two channels of EEG were recorded with silver/silver chloride electrodes applied with collodion in the F4-P4, F3-P3 positions (impedances <5 kohms).

Initial recordings were made within 48 hours of birth, transfer to the neonatal unit, or onset of the illness (if delayed). Sequential recordings were made for 24 hour periods at intervals of two to four weeks until term or discharge from the unit. Data for each 24 hour period were recorded on standard C 120 cassette tape and reviewed on a visual display unit of Medilog system at 20 and 60 times the normal speed at scales of 1·5 and 3·0 cm/second.

Compressed transcription was done at 6 cm/minute using a Siemens 8 Elema Schonander ink jet recorder. All initial recordings were assessed independently by two observers without knowledge of the ultrasound development or clinical outcome.

Classification of normal or abnormal was made from standards for gestational age established for the Medilog 4–24 monitor in a group of low risk preterm infants,[7] as well as from criteria derived from conventional EEG recordings.[8]

EEG abnormalities were classified into four categories (fig 1), as follows:

(1) Activity inappropriate for gestation. In preterm infants this was indicated by excess discontinuous activity or a prolonged interburst interval for gestational age, and in term infants by impaired sleep state definition.

(2) Overtly abnormal activity independent of gestation (excluding seizures) as indicated by persistent discontinuity throughout recording or burst suppression; low amplitude recording; asymmetry; asynchrony, and spikes and sharp waves.

These were further classified according to background activity into those showing: (i) one abnormal feature on normal background; (ii) those showing one abnormal feature on category 1 abnormal background; and (iii) those showing two or more overtly abnormal features.

(3) Seizures were further classified according to background activity into; (i) those on normal background; (ii) those on category 1 abnormal background; and (iii) those on category 2 abnormal background.

(4) Maximal background depression either (i) with seizures or with (ii) no discernible activity.

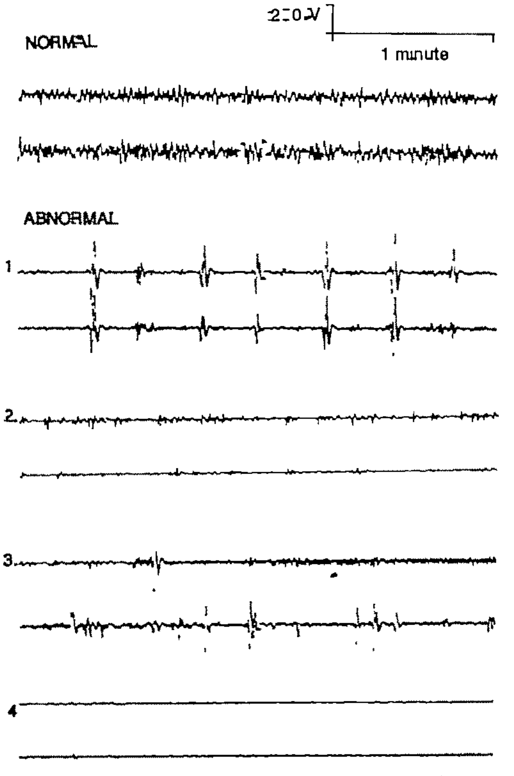

Fig 1 *Examples of categories of EEG abnormality (compressed time scale) preceded for contrast by normal preterm record during phase of continuous activity.*

### NEUROLOGICAL ASSESSMENT OF OUTCOME

Assessment of outcome was made on clinical examination at discharge from the neonatal unit using a standardised protocol,[9] and at 6–18 months using the Griffiths mental development scale and items from Amiel-Tison's[10] and Touwen's[11] scores.

Because some infants have been assessed only up to the age of 6 months, only major neurological abnormalities were considered in this study. These included confirmed cerebral palsy and mental retardation.

## Results

The table summarises the development of the ultrasound appearances, the initial and sequential EEG findings, and the clinical outcome in the 31 infants studied. The relative timings of the development of the EEG and ultrasonographic abnormalities are also shown

### ULTRASOUND ASSESSMENT

In 19 of the infants studied the densities resolved without cyst formation, but in seven they proceeded to extensive cystic leucomalacia. In five infants the cysts were already well established at presentation. Of the 12 infants with cysts, eight had periventricular leucomalacia and four had subcortical leucomalacia.

### EEG ASSESSMENT

In 13 infants the initial EEG recording was abnormal (fig 2). Category 4 abnormalities were found in four infants, two of whom presented with subcortical leucomalacia and two of whom subsequently

Table *Summary of ultrasound development, initial and sequential EEG findings, and outcome in 31 infants with echodense lesions on ultrasonography*

| *Case No* | *Ultrasound development* | *Initial EEG category* | *Sequential EEG category* | *Outcome* |
|---|---|---|---|---|
| 1 | Cysts. subcortical leucomalacia | 4 (ii) | Not done | Died |
| 2 | Cysts subcortical leucomalacia | 4 (ii) | Not done | Died |
| 3 | Cysts subcortical leucomalacia** | 4 (i) | 3 (iii) | Abnormal |
| 4 | Cysts subcortical leucomalacia** | 4 (i) | 3 (iii) | Abnormal |
| 5 | Cysts periventricular leucomalacia* | 3 (iii) | Not done | Died |
| 6 | Cysts periventricular leucomalacia* | 3 (iii) | 2 (ii) | Died |
| 7 | Cysts periventricular leucomalacia | 3 (iii) | 2 (ii) | Abnormal |
| 8 | Cysts periventricular leucomalacia | 2 (iii) | Not done | Abnormal |
| 9 | Cysts. periventricular leucomalacia* | 2 (ii) | Normal | Abnormal |
| 10 | Cysts periventricular leucomalacia** | 1 | 3 (i) | Died |
| 11 | Cysts. periventricular leucomalacia | Normal | Not done | Abnormal |
| 12 | Cysts: periventricular leucomalacia | Normal | Normal | Abnormal |
| 13 | Densities only | 3 (iii) | Not done | Died |
| 14 | Densities only | 3 (iii) | 3 (i) | Abnormal |
| 15 | Densities only | 2 (iii) | Not done | Abnormal |
| 16 | Densities only | Normal | Not done | Normal |
| 17 | Densities only | Normal | Not done | Normal |
| 18 | Densities only | Normal | Not done | Normal |
| 19 | Densities only | Normal | Not done | Normal |
| 20 | Densities only | Normal | Not done | Normal |
| 21 | Densities only | Normal | Not done | Normal |
| 22 | Densities only | Normal | Not done | Normal |
| 23 | Densities only | Normal | Not done | Normal |
| 24 | Densities only | Normal | Normal | Died |
| 25 | Densities only | Normal | Normal | Normal |
| 26 | Densities only | Normal | Normal | Normal |
| 27 | Densities only | Normal | Normal | Normal |
| 28 | Densities only | Normal | Normal | Normal |
| 29 | Densities only | Normal | Normal | Normal |
| 30 | Densities only | Normal | Normal | Normal |
| 31 | Densities only | Normal | Normal | Normal |

*EEG abnormality preceded cysts, **EEG abnormality preceded densities

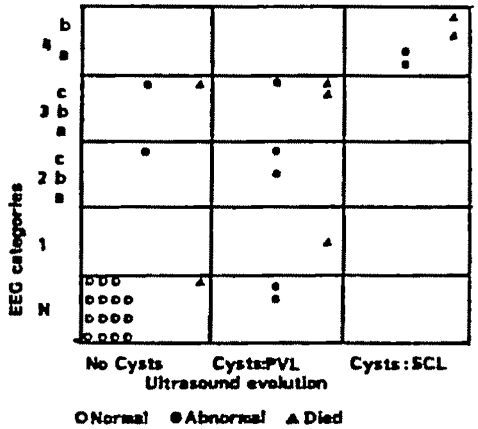

Fig 2 *Correlation of initial EEG, ultrasound evolution of densities, and neurological outcome in 31 infants*

developed it. Eight infants had category 2 and 3 abnormalities, five of which were associated with cystic lesions. Two of these had presented with periventricular leucomalacia and another three subsequently developed it. The remaining three infants with category 2 and 3 abnormalities did not develop cysts. Only one infant had category 1 abnormalities and he subsequently developed periventricular leucomalacia. The EEG abnormality preceded the appearance of even the density in three of the above infants; two of these subsequently developed subcortical leucomalacia and one periventricular leucomalacia. Fig 3 shows the progression in one of these infants.

Eighteen infants had normal EEG recordings. Of these 16 did not form cysts; one had presented with periventricular leucomalacia and one subsequently developed it.

Six infants had persistently abnormal EEG recordings (fig 4), including two with subcortical leucomalacia, three with periventricular leucomalacia, and one without cysts. Ten infants had normal sequential EEG recordings. In one infant with periventricular leucomalacia an initially abnormal recording became normal within two weeks. Nine infants had persistently normal EEG recordings,

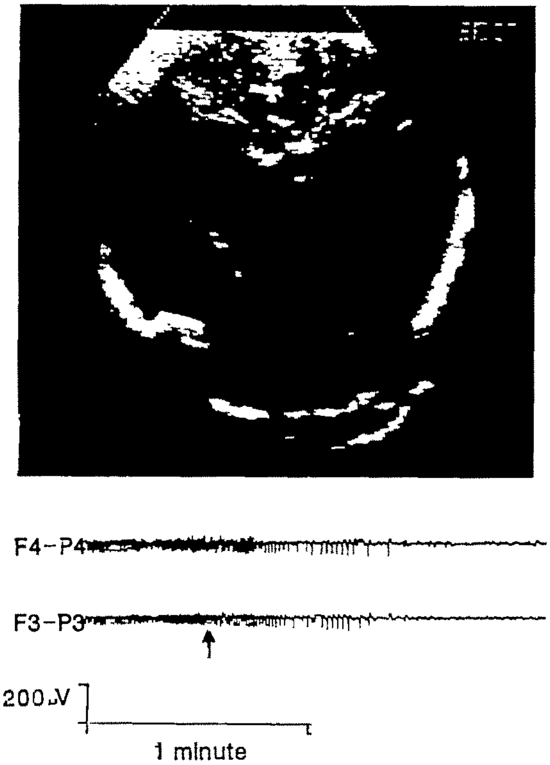

Fig 3(a) *Relative evolution of EEG and ultrasound abnormalities of subcortical leucomalacia in 35 week gestation infant with necrotising enterocolitis (case 3) Day 1, ultrasound within normal limits; EEG severely abnormal with bilateral seizures (arrowed) on very low amplitude background*

including eight without cysts and one with periventricular leucomalacia.

Eight infants showed seizure activity on EEG recording (categories 3 and 4), including two with subcortical leucomalacia, four with periventricular leucomalacia, and two without cysts. These were associated with clinical seizures in five infants.

NEUROLOGICAL OUTCOME

Eight infants died too early for assessment and nine of the 23 survivors developed abnormally.

CORRELATION OF EEG WITH CLINICAL OUTCOME

The two survivors who showed category 4 abnormalities on the initial EEG recordings had the most severe neurological abnormalities (fig 2). Category 2 and 3 abnormalities were associated with abnormal outcome in seven surviving infants. Category 1 abnormality was found in only one infant who died

A normal initial EEG recording was not invariably associated with a normal outcome; two sur vors had normal initial recordings but abnorm outcome.

If the sequential EEG recordings were persi ently abnormal the outcome was always abnorm four survivors in whom this occurred were all neur logically abnormal. Not all infants with a norm sequential EEG had a normal outcome, howeve Neither persistently normal recordings nor on which subsequently became normal were constant associated with normal outcome. This happened seven survivors, in two of whom the outcome w abnormal

Seizures, present in four infants, always result in abnormal outcome.

**Discussion**

EEG recordings in neonates have been shown other conditions[12 13] to give early and sensiti

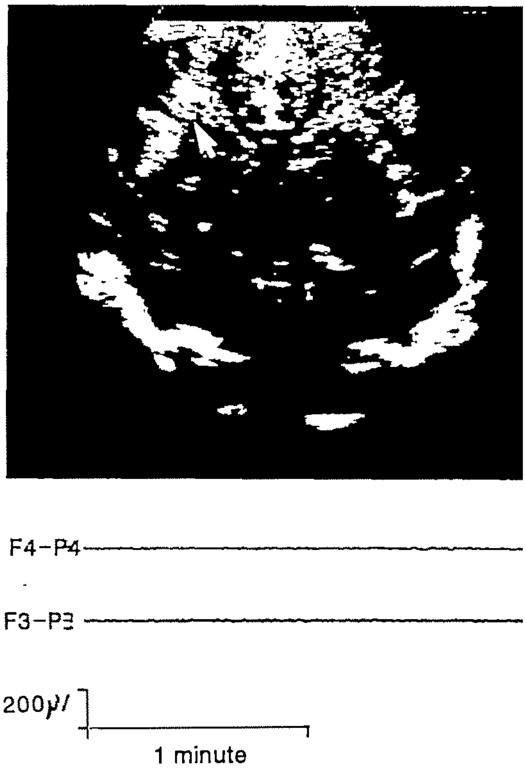

Fig 3(b) *Relative evolution of EEG and ultrasound abnormalities of subcortical leucomalacia in 35 week gestation infant with necrotising enterocolitis (case 3) Day 5, ultrasound now abnormal with echodensities in periventricular regions and inter-hemispheric fissure, EE persistently abnormal with extreme amplitude depression.*

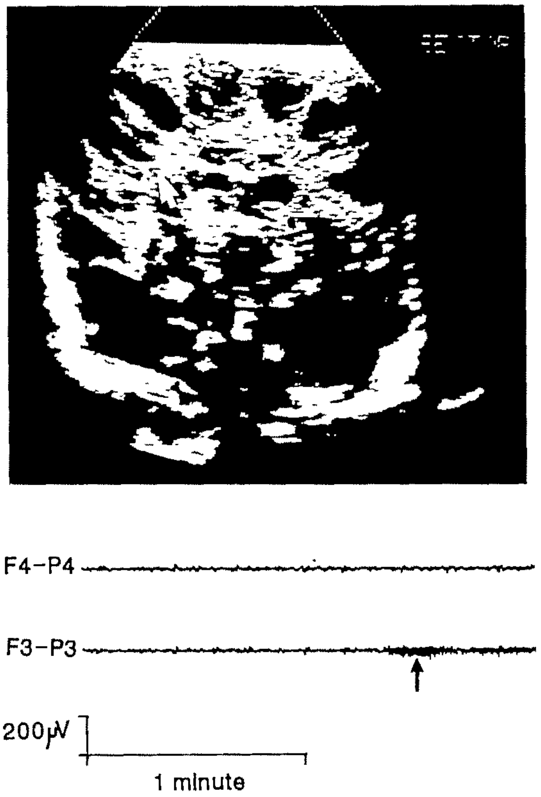

Fig 3(c) *Relative evolution of EEG and ultrasound abnormalities of subcortical leucomalacia in 35 week gestation infant with necrotising entercolitis (case 3). Week five, ultrasound now shows extensive subcortical leucomalacia, EEG still low amplitude and discontinuous with persistent seizures (arrowed)*

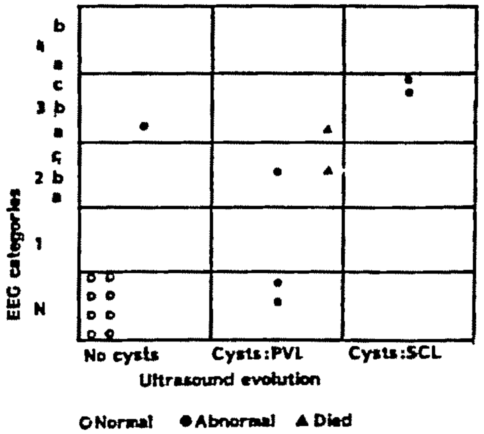

Fig 4 *Correlation of sequential EEG, ultrasound evolution of densities, and neurological outcome in 16 infants*

indications of the functional severity of lesions of considerable prognostic importance This study shows that the technique may also be applied to the recently recognised problem of whether ultrasound echodensities indicate cystic leucomalacia

In this condition the EEG recording also provided a sensitive guide to the functional severity of the ultrasonographic lesion, showing much more frequent and serious abnormalities in infants with cystic leucomalacia than in those whose densities resolved without cysts In particular, it identified the exceptional severity of the functional damage associated with subcortical leucomalacia. Maximal depression of background EEG activity was seen in the four infants with subcortical leucomalacia but in no other group.

The sensitivity of the initial EEG abnormality as an index of the functional severity of the lesion was also reflected in its prognostic ability. Although there was a definite correlation between EEG abnormalities and abnormal outcome, a normal EEG recording was not invariably associated with a normal clinical outcome. It is possible that with only two channels of EEG recording some abnormal foci may have been missed Alternatively, the EEG recording may have shown some recovery after the initial insult. In favour of this argument is the fact that improvement or return to normal of an initially abnormal EEG recording was seen in seven infants in sequential studies. Two infants had normal initial recordings and abnormal outcome. One of these was studied late when cysts were already present. The other had densities from day 1 after a pregnancy complicated by severe pre-eclamptic toxaemia. It is therefore possible that the EEG, which was also monitored from day 1, may already have become normal by the time of the birth after an insult in utero.

In contrast, the particular prognostic value of an abnormal EEG recording is well illustrated by this study. Seizures always indicated an abnormal outcome. Even in the absence of seizures, however, abnormalities such as low amplitude and excessive discontinuous background activity, and asymmetry and asynchrony of discharges, were consistently adverse prognostic factors, irrespective of ultrasonographic findings

The particular additional value of EEG monitoring was that the prognostically relevant information that it supplied was immediately available from the first day of recording, whereas that derived from ultrasonography was not available for two to four weeks when the densities had resolved or cysts had formed.

Neonatal EEG recordings may be effectively monitored using the four channel Medilog 4–24 continuous recorder in infants who have ultrasound echodensities and cystic leucomalacia, the information that the recordings provide acts as a sensitive index of the severity of such lesions. The early appearance of these important EEG changes means that the role of this investigation is not confined merely to confirming the ultrasound assessment. Rather it provides the first available guide to assessing the functional severity of these lesions and their prognostic importance.

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# Specific enlargement of the fourth ventricle after ventriculo-peritoneal shunt for post-haemorrhagic hydrocephalus

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SUMMARY Disproportionate enlargement or isolation of the fourth ventricle are rare complications of ventriculo-peritoneal shunt for post-haemorrhagic hydrocephalus. Obvious features such as ataxia may indicate raised intracranial pressure in the posterior fossa. The child may, however, present with less specific signs of vomiting, anorexia, and lethargy and these symptoms may be misinterpreted as secondary to dilation of the lateral ventricular system due to malfunction of the ventriculo-peritoneal shunt. Two children with disproportionate enlargement of the fourth ventricle and two children with isolation of the fourth ventricle are described to illustrate the wide variations in clinical presentation. These rare complications can be diagnosed by real time ultrasound examination of the brain or computed tomography of the head. They should be considered in the differential diagnosis of a child who deteriorates after lateral ventriculo-peritoneal shunting for post-haemorrhagic hydrocephalus, and dealt with specifically to avoid the risk of upward herniation of the enlarged fourth ventricle.

Intracranial haemorrhage is a common problem in the premature neonate and occurs in up to 70% of infants who are born at less than 35 weeks' gestation, weigh less than 1500 g, and require assisted ventilation.[1] Post-haemorrhagic hydrocephalus may result from inflammatory ependymitis; basilar arachnoiditis; obstruction of the foramen of Munro, aqueduct of Sylvius, or fourth ventricular outflow foramina;[2] or occlusion and scarring of surface absorptive mechanisms.[3] Many infants require ventricular cerebrospinal fluid shunting to control the dilatation of the ventricles[4] and there is substantial morbidity associated with progressive post-haemorrhagic hydrocephalus.[5] Intraventricular haemorrhage may also occur in the infant born at term; 35% subsequently require ventricular shunting.[6]

We described three premature infants and one infant born at term who required lateral ventricular shunting for control of post-haemorrhagic hydrocephalus and who subsequently developed the rare complication of specific enlargement of the fourth ventricle. They illustrate a breadth of presentation and management and are discussed in the context of published experience.

## Case reports

### CASE 1

This infant was delivered at 30 weeks by caesarean section because of severe maternal pre-eclampsia. He did not breathe spontaneously at birth and required immediate intermittent positive pressure ventilation. His need for respiratory support increased and at 28 hours his condition deteriorated sharply; ultrasonographic examination showed a grade four intraventricular haemorrhage.

He needed artificial ventilation for some weeks and at the age of 2 months he was referred for further management of post-haemorrhagic hydrocephalus. Three days later he had a ventriculo-peritoneal shunt inserted. At first his postoperative course was uncomplicated, but three weeks later he developed paroxysmal episodes of cyanosis with respiratory irregularities; ultrasound examination of the ventricular system showed no increase in enlargement of the lateral and third ventricles but a disproportionate increase in the size of the fourth ventricle (fig 1).

Intracranial pressure was measured from the right lateral ventricle and was 1·07 kPa. A small amount

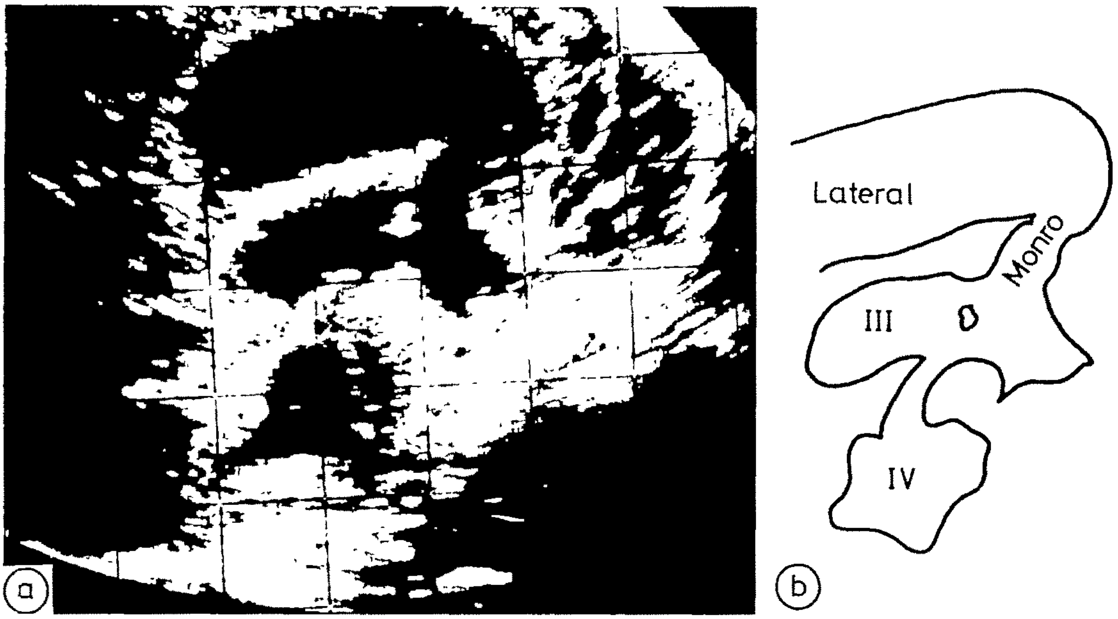


Fig 1 a & b *Case 1: disproportionate enlargement of fourth ventricle on real time ultrasonography.*

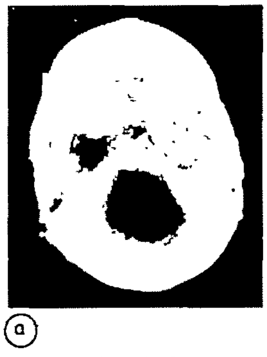
of ventricular fluid was withdrawn. Thereafter his respiratory abnormalities resolved, and follow up ultrasonographic examination showed resolution of the enlargement of the fourth ventricle. Subsequently the infant made good progress, and at the age of 18 months showed normal development apart from slight delay in motor development with a degree of ataxia.

CASE 2

This infant was delivered at term by spontaneous vertex delivery There was no asphyxia at birth, she was breast fed, and given vitamin K supplements. She was admitted at the age of 3 weeks with an acute history of irritability, vomiting, and opisthotonus and was shown to have bilateral haemorrhages into the ventricular system Two weeks later a Rickham reservoir was inserted into the right lateral ventricle, but daily removal of cerebrospinal fluid failed to control her intracranial pressure and she had a theco-peritoneal shunt inserted.

At the age of 4½ months computed tomography of the head showed marked ventricular enlargement and her theco-peritoneal shunt was replaced with a ventriculo-peritoneal shunt. After operation she developed ventriculitis, and *Escherichia coli* was isolated from the lumbar and ventricular cerebrospinal fluid. She required seven shunt revisions over the next four years.

When she was 4½ years old, she was admitted with acute pain down the left side of her neck associated with torticollis and vomiting. It was impossible to measure intracranial pressure because of the occluded Rickham reservoir. Computed tomography showed enlargement of the right lateral ventricle with obvious enlargement of the fourth ventricle. (fig 2a). Revision of the right ventriculoperitoneal shunt was performed with subsequent decrease in the size of the fourth ventricle and resolution of her symptoms. (fig 2b).



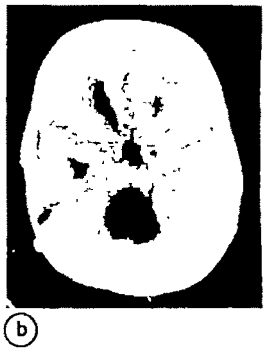


Fig. 2a *Case 2. disproportionate enlargement of fourth ventricle.*

Fig. 2b *Case 2 disproportionate enlargement of fourth ventricle less marked after revision of lateral ventriculoperitoneal shunt.*

CASE 3
This baby boy was delivered by emergency caesarian section at 34 weeks after a concealed placental haemorrhage. He was asphyxiated at birth and received full intensive care to minimise secondary brain swelling. During his early course he was hypoglycaemic and had tonic convulsions. On the fifth day he sustained a bowel perforation caused by necrotising enterocolitis. On day 13 he was noted to have post-haemorrhagic hydrocephalus. Ventricular taps and removal of cerebrospinal fluid had no effect and initially he had a theco-peritoneal shunt inserted; this blocked after 38 hours and he then had a lateral ventriculo-peritoneal shunt performed.

Follow up ultrasonography showed good control of his hydrocephalus. At the age of 8 months he was admitted with ventriculitis due to *Staphylococcus albus*, for which he was treated with intravenous and intrathecal gentamicin and flucloxacillin and shunt revision. At this time he had cerebral palsy with a diplegia and a right hemiplegia and microcephaly

At the age of 3 years 4 months he was readmitted with a one week history of anorexia and drowsiness There was no change in his neurological condition but intracranial pressure monitoring carried out through his left Rickham reservoir showed intermittent high pressure readings of 2·67 kPa. There was a history of a minor head injury one month before his admission Computed tomography showed obvious enlargement of the fourth ventricle with small lateral ventricles and a small third ventricle (fig 3a). He underwent posterior fossa craniectomy with exploration of the large fourth ventricle and insertion of a cysto-peritoneal shunt. Postoperatively computed tomography showed considerable reduction in the size of the fourth ventricle (fig 3b) and his symptoms resolved.

CASE 4
This baby girl was delivered by spontaneous vertex delivery at 28 weeks; no asphyxia or respiratory distress was noted at birth. Her occipitofrontal circumference increased abnormally suggesting the development of hydrocephalus, and an ultrasound examination at 2 months of age showed gross enlargement of both lateral ventricles and a left porencephalic cyst. At the age of 2 months a ventriculo-peritoneal shunt was inserted. A month later isolated enlargement of the fourth ventricle was detected on ultrasound examination. At the age of 6 months she had a left hemiparesis

When she was 9 months old she presented with paroxysmal episodes of right sided weakness associated with fever, and computed tomography showed that the lateral ventricles were not grossly enlarged and the third ventricle was small and displaced. There was a large cystic area in the posterior fossa comprising the grossly distended

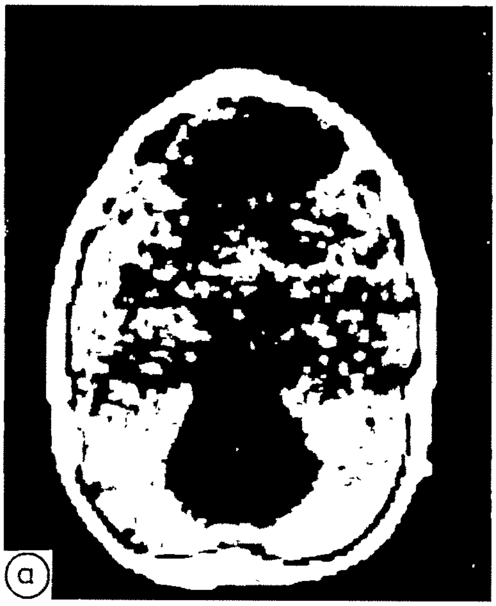


Fig. 3a *Case 3 isolated enlargement of fourth ventricle.*

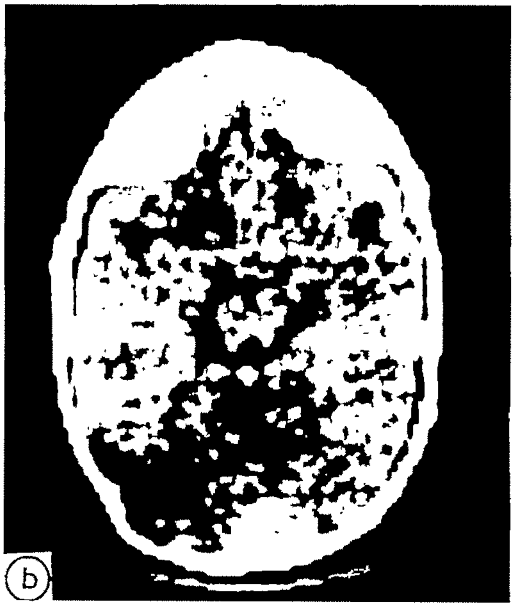
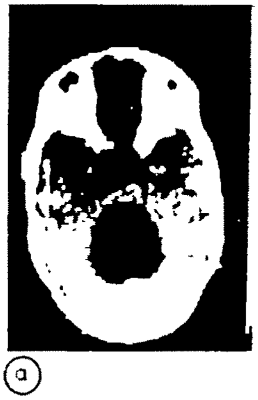


Fig 3b *Case 3 resolution of enlargement of fourth ventricle after cysto-peritoneal shunt diversion*



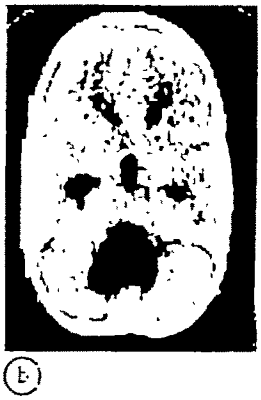


Fig 4a *Case 4. isolated enlargement of fourth ventricle.*

Fig. 4b *Case 4 reduction in size of fourth ventricle after cysto-peritoneal shunt diversion*

fourth ventricle, and there appeared to be no obvious communication between the fourth ventricle and the supratentorial ventricular system. Her right hemiparesis resolved completely on conservative management.

Four months later she was admitted with an acute attack of anorexia and vomiting. Clinical examination revealed neck retraction, hypertension, and bradycardia. Intracranial pressure measured through a right lateral ventricle Rickham reservoir was 1·33–1·50 kPa. Computed tomography showed persisting enlargement of an isolated fourth ventricle (fig 4a) and a cysto-peritoneal shunt was inserted. Follow up computed tomography (fig 4b) showed an improvement in the size of the ventricle and the raised intracranial pressure in the posterior fossa had resolved

## Discussion

Specific enlargement of the fourth ventricle can take the form of a disproportionate enlargement or a complete isolated encystment, and although the presentation of the two conditions may be similar in children who have had shunts inserted for post-haemorrhagic hydrocephalus the management is quite different.

In disproportionate enlargement of the fourth ventricle the aqueductal canal is patent and this can be shown using air contrast studies or Conray ventriculography, whereas the foramina of Luschka and Megendi are occluded.[7] The abnormality arises when this type of occlusion occurs at the same time as abnormal weakness of the brain stem parenchyma around the fourth ventricle. Collision of cerebrospinal fluid against the obstruction produces a 'water hammer' effect and results in enlargemen of the fourth ventricle. This disproportionat enlargement can be detected by real time ultrasonography of the posterior fossa[8] or computed tomography of the head.

The presenting symptoms of both the cases with this condition suggested raised pressure in the posterior fossa with bradycardia and respiratory irregularities prominant in case 1, and neck pain and torticollis in case 2. Although the intracranial pressure was not raised in case 1 when measured through a Rickman reservoir in his right lateral ventricle, hi symptoms resolved when cerebrospinal fluid wa removed from the lateral ventricle. In case 2 the disproportionate enlargement of the fourth ventricle improved and she became asymptomatic afte revision of her lateral ventriculoperitoneal shunt Presumably these forms of management are effective because the enlarged fourth ventricle remains in communication with the rest of the ventricular system.

The fourth ventricle may, however, become completely isolated from the rest of the ventricula system when both the aqueduct of Sylvius and the exit foramina of Lushka and Magendi are occluded. This acquired condition must be distinguished from other cystic malformations of the posterior fossa.[1] It is never a primary disease in that it occurs only after shunting of the lateral ventricular system fo communicating hydrocephalus, aqueduct stenosis or obstruction to the outlets of the fourth ventricle[1] and only in the presence of the foreign body of the shunt.

The initial reports of the condition were i patients who had communicating hydrocephalu after infections of the central nervous system.[12 1] Even in the children who develop the condition afte shunting for post-haemorrhagic hydrocephalus the likelihood of isolation of the fourth ventricle developing is greater if they have had episodes o ventriculitis and many children have had multiple shunt revisions.[14]

Isolation of the fourth ventricle may be associated with clinical signs of an expanding lesion in the posterior fossa and ataxia, neck retraction, torticollis nystagmus, diplopia, and dysarthria should alert a clinician to the condition in children who have previously had a shunt inserted for post-haemorrhagic hydrocephalus. Not only might the symptoms be o a non-localising nature, for example, anorexia and lethargy,[9] but a subtle deterioration may be difficul to detect in these children, who often have severa handicaps, and therefore a high index of suspicion i required.

Measurement of the intracranial pressure through a reservoir in the lateral ventricle does not alway help: it was raised in one of our cases and normal in another. If the intracranial pressure is measured directly from the fourth ventricle, however, it is raised in symptomatic cases.[15] As the fourth ventricle is completely isolated from the rest of the ventricular system, a mistaken diagnosis of malfunction of the lateral ventriculoperitoneal shunt leading to subsequent revision of the shunt may lead to upward herniation of the enlarged fourth ventricle, whereas independent shunting of the cystic ventricle results in control of the condition.[9 11]

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# Ductus arteriosus blood flow during first 48 hours of life

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SUMMARY A volumetric Doppler technique was used to measure net ductus arteriosus shunt during the first 48 hours of life in 30 infants of less than 33 weeks' gestation, and in 10 full term infants. In the full term infants a left to right shunt of 62 ml/kg/minute (95% confidence limits 43–82) shortly after birth decreased rapidly over the first 12 hours and was not measurable by 48 hours. The preterm infants had smaller left to right shunts shortly after birth—49 ml/kg/minute (95% confidence limits 38–59). There was no obvious subsequent change in the mean shunt, although by 48 hours there was greater variation in the size of the shunt. The respiratory distress syndrome did not affect the size of the ductal shunt, but the shorter the gestation period the larger the shunt by 48 hours. A ductal flow of greater than 70 ml/kg/minute at 48 hours of age predicted the subsequent development of a ductal murmur with 75% sensitivity and 100% specificity.

During intrauterine life the ductus arteriosus shunts blood right to left, away from the high resistance pulmonary circulation into the descending aorta. After delivery vascular resistance and pressure fall rapidly in the pulmonary circulation and rise in the systemic circulation. The reversal of the pressure gradient across the ductus arteriosus leads to a net left to right shunt until functional closure of the ductus occurs. In preterm infants closure of the ductus is often delayed, leading to persisting left to right or bidirectional shunts that may decrease lung compliance, increase the work load of the left ventricle, and decrease perfusion of the myocardium and other systemic vascular beds.[1] During the early days of life these ductal shunts are not usually accompanied by the cardiac murmur which is characteristic of them after the first week.[2 3]

The time of closure of the ductus arteriosus has been studied at necropsy,[4] and by various catheterisation[1 5–6] and echocardiographic[7] techniques. These techniques are either invasive and difficult to interpret,[8] or are sensitive to small and functionally irrelevant jets of blood flowing through the ductus arteriosus. This study quantitatively compared the time course of ductal shunting in both full term and preterm infants during the first 48 hours of life.

## Patients and methods

The velocity of blood flowing within the aorta may be calculated from the frequency shift of ultrasound scattered back from moving blood corpuscles according to the formula:

$$\text{velocity} = \text{frequency shift} \times c / 2f\cos A$$

where c = speed of ultrasound in tissue (1500 cm/second); f = frequency of ultrasound, and A = Doppler angle.

If the aorta is evenly covered by the ultrasound beam then the average time and spatial velocity may be derived from the frequency power spectrum of the shifted Doppler signal. By using the full power spectrum, the average velocity may be accurately calculated, irrespective of variation in the velocity profile across the vessel lumen. Volume flow is the product of average velocity and aortic cross sectional area. If flow is measured in this way just above and just below the origin of the ductus arteriosus then net ductal flow may be calculated by subtraction.

In this study a duplex ultrasound scanner (ATL Mk 600) was used to identify the aorta and locate the pulsed Doppler sample volume and measure the Doppler angle using the real time image. The scanner was interfaced to a microcomputer (Apple IIe), and the full Doppler power spectrum from about five cardiac cycles was fed into the memory before being processed to remove noise and the calculation of the average velocity was made; it was then stored on disc. A 5 mm pulse gate and 100 Hz wall filter were used. Imaging was performed at 7·5 MHz and Doppler studies at 5 MHz. The Doppler sample volume was placed in the proximal ascending aorta from a substernal four chamber view, in the preductal aorta from a suprasternal or left supraclavicular long axis view, and in the postductal aorta close to the diaphragm from a low substernal long axis view. The combination of a discrete pulsed Doppler sample volume and duplex Doppler imaging allowed us to confirm the precise origin of the Doppler signals.

The aortic diameter at the three sites of Doppler velocity sampling was measured using precordial M mode imaging from which the area could be calculated by assuming a circular cross section. Perpendicular preductal aortic M mode measurements were sometimes impossible; measurements were then made from the real time image. These usually correlated closely with the M mode measurements made postductally.

Volume flow Doppler systems are susceptible to both systematic and random errors. Systematic errors are usually due to the preferential sampling of central stream velocities. These were minimised in this study by calibrating the system in the laboratory using a range of vessel diameters in a pulsatile flow rig that was filled with human blood. Errors in the measurement of vessel diameter and Doppler angle are usually random and their effect was diminished by taking the mean of at least four recordings from each site.

The Wilcoxon signed rank matched pairs, Mann-Whitney U (2 tailed) or Fisher's exact tests were used as appropriate to calculate the significance of differences.

The group born at term comprised 10 infants of greater than 37 weeks' gestation who had no perinatal problems (range 38–41 weeks, median 40 weeks; birth weight 2730–3960 g, median 3275 g). Those infants who were bottle fed received 60 and 90 ml/kg/day on the first and second days of life, respectively.

The preterm group comprised 30 infants born at the Bristol Maternity Hospital between June 1985 and January 1986 at 33 completed weeks of gestation or less. Those with congenital malformation (range 24–32 weeks, median 30 weeks, birth weight 760–2140 g, median 1430 g) were excluded. Table 1 summarises their clinical characteristics. A standard fluid regimen of 60–80 and 90–120 ml/kg/day was given on the first and second days of life, respectively.

To assess the effect of respiratory distress the mean of the alveolar to arterial oxygen gradients at the time of each study was calculated. A division point of 200 mm Hg was arbitrarily chosen to separate the infants with moderate or severe respiratory disease from those with mild or absent disease. To eliminate bias due to gestational age we matched 13 infants from each group to within one week.

Doppler recordings were made initially between 1 and 2 hours of age, and then at 6 hours (in the preterm group only), 12 hours, 24 hours, and 48 hours of age. Parental consent was obtained before Doppler examination of both term and preterm infants.

## Results

In the term infants the mean ductal shunt at 1–2 hours of age was 62 ml/kg/minute left to right (95% confidence limits 43 to 82). Over the first 12 hours of life the shunt had reduced to 14 ml/kg/minute (95% confidence limits $-6$ to $+33$, $p = 0{\cdot}005$), and by 48 hours to 0·5 ml/kg/minute (95% confidence limits $-10$ to $+11$, $p = 0{\cdot}005$) (figure).

In the preterm infants the mean ductal shunt at 1–2 hours was 49 ml/kg/minute left to right (95% confidence limits 38 to 59, significantly less than the shunt in the term group, $p = 0{\cdot}04$). Over the following 48 hours there was no significant change in the size of the mean ductal shunt. There was, however, a progressive fall in the median size of

Table 1 *Clinical characteristics of 30 preterm infants studied*

| *Clinical feature* | *No of cases* |
|---|---|
| Sex (M F) | 13.17 |
| Reason for delivery | |
| Spontaneous preterm labour | 18 |
| Antepartum haemorrhage | 5 |
| Prolonged rupture of membranes | 6 |
| Hypertension | 1 |
| Delivery (vaginal caesarian section) | 18 12 |
| Maternal drugs during labour or delivery. | |
| General anaesthesia | 10 |
| Epidural anaesthesia | 7 |
| Opiate analgesia | 3 |
| Oxytocin | 3 |
| Singletons twins | 22 8 |
| Respiratory distress syndrome | 16 |
| Respiratory support during first 48 hours | |
| Positive pressure ventilation | 22 |
| Continuous positive airways pressure | 5 |
| Received muscle paralysis | 3 |
| Survived to hospital discharge | 29 |

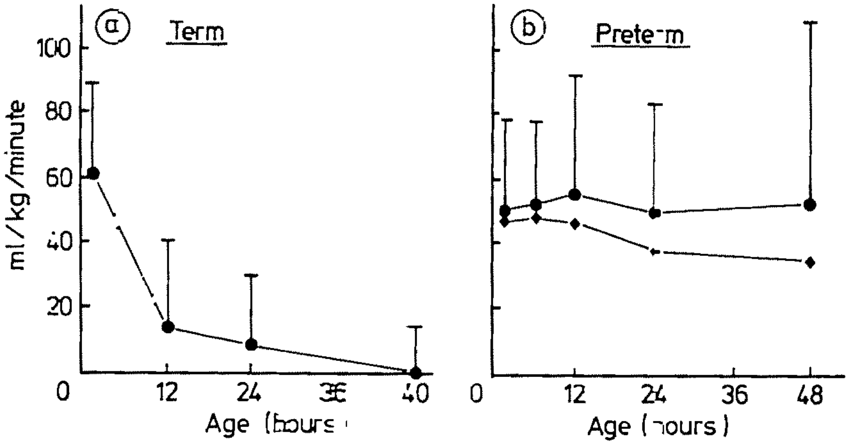

Figure *Net ductal flow (ml/kg/minute) in term (n=10) and preterm (n=30) infants during first 48 hours of life. Flow left to right expressed as positive. Points represent mean (SD) (●) or median (◆).*

ductal shunt and a progressive widening of the variety of sizes of shunts (figure). The ductal shunts in the preterm infants were significantly greater than in the term infants from 12 hours of age (p=0·0008).

There was no significant difference in size of ductal shunt at any age between the matched groups with severe and mild or absent respiratory distress (table 2).

Shortly after birth there seemed to be no difference dependent on gestational age in the size of ductal shunt. Although there were only four infants of less than 27 weeks' gestation surviving at 48 hours of age, three of them had ductal shunts greater than 70 ml/kg/minute (one as large as 212 ml/kg/minute). Of the remaining 24 infants studied of gestational age from 27 to 33 weeks (one infant was too unstable to study at 48 hours), only three had ductal shunts greater than 70 ml/kg/minute at 48 hours (correlation coefficient between shunt at 48 hours and gestational age, r = −0·47, p = 0·01).

During the study no cardiac murmurs were heard, but nine infants subsequently developed characteristic ductal murmurs. Of the 28 infants studied at 48 hours of age, all of the six with ductal shunts of greater than 70 ml/kg/minute went on to develop murmurs, while only two with smaller shunts at 48 hours later developed murmurs (sensitivity 75%, specificity 100%; Fisher's exact test p = 0·0001).

Table 2 *Median ductal shunts in respiratory distress syndrome (ml/kg/minute)*

| *Extent of respiratory distress syndrome* | *Age (hours)* | | | | | |
|---|---|---|---|---|---|---|
| | *1·5* | *6* | *12* | *24* | *48* | *Mean (0–48)* |
| Minimal | 50 | 47 | 30 | 51 | 32 | 43 |
| Severe | 42 | 55 | 50 | 35 | 37 | 38 |

## Discussion

Doppler ultrasound offers a safe and non-invasive technique for the assessment of the circulation in newborn infants. It has been used to investigate the cerebral circulation,[9] for the measurement of cardiac output,[10] and in the diagnosis of congenital heart disease.[11] This study extends the latter application by measuring flow in the aorta above and below the level of the ductus arteriosus, thus allowing calculation of the net flow through the duct by subtraction. A similar technique has been used to assess bloodflow to the head and neck.[12] Direct Doppler measurement of flow within the ductus is not feasible as angle and diameter are rarely measurable from the real time image.

The major limitation of volume-flow Doppler techniques is its lack of accuracy[13]; this assumes even greater importance when two measured flows are subtracted as in this study. Systematic error was minimised by laboratory calibration of the system using a pulsatile flow rig in which blood flow could be precisely, accurately, and independently measured. Random error in volumetric Doppler methods derives mainly from inaccuracy of the measurement of the Doppler angle and the vessel diameter.[13] Error from both sources was minimised by making multiple measurements at each site and by comparing flow sequentially in groups of infants

This new technique provides physiological information which cannot otherwise be obtained without unjustifiably invasive techniques. It may also provide useful clinical information about the size of large ductal shunts in individual patients, but with current machines it is time consuming, requires great care, and is progressively less accurate the smaller the ductal shunt. Doppler techniques that use an analysis of wave form shape may be more useful for routine clinical assessment of the size of ductal shunts.[14 15]

The technique used in this study measures the net ductal shunt integrated over several seconds. The measurement of a net left to right shunt in an infant does not preclude there being a right to left component at some point in the cardiac cycle. At the time of the first study (between 1 and 2 hours of age) in both term and preterm infants the net ductal shunt was left to right, even in the presence of the respiratory distress syndrome. This confirms previous reports that the major right to left cardiac shunt in preterm infants with the respiratory distress syndrome is at atrial rather than ductal level.[16] Placing the Doppler sample volume within the ductus itself shows that initially the flow is bidirectional—right to left in early systole, becoming left to right in late systole and diastole—confirming previous studies using catheters [17]

The size of the ductal shunt is determined by the pressure gradient between the systemic and pulmonary circulations, the degree of ductal constriction, and possibly by the angle at which the ductus joins the aorta. The net left to right shunt indicates that the mean pulmonary artery pressure is below the systemic pressure even in respiratory distress syndrome. The relatively smaller shunt shortly after birth in the preterm group, compared with that of the term group, probably represents a decreased aortopulmonary gradient due to delayed fall in pulmonary artery pressure.

As far as we know this is the first report of a non-invasive volumetric technique to measure the rate of closure of the ductus arteriosus. The rapid diminution in ductal shunt in the term infants must reflect the rapid closure of the ductus itself The time to closure is shorter than has been suggested in other studies, which have looked qualitatively at the effect of the ductal shunt on the pulmonary artery waveform.[7] These studies may have been measuring small and functionally irrelevant ductal jets that cause disproportionately large disturbances within the pulmonary artery. In the preterm group no change in mean ductal flow over the first 48 hours, a progressive decrease in median flow, and an increase in variance within the group indicate that in most infants there was some decrease in shunting, but that this was balanced by a few infants in whom the size of the shunt progressively increased. Although the numbers were small, it seemed that the infants with increasing shunts were usually younger than those in whom they decreased Interestingly, in this study, contrary to some previous reports,[1 18] we found that the respiratory distress syndrome did not influence the size of shunt or rate or ductal closure. The previous studies, however, did not attempt to separate the independent influences of prematurity and respiratory distress syndrome. Either the latter has no effect on ductal tone, or the effects of persisting ductal patency are counteracted by increased pulmonary vascular tone.

This study confirms previous reports of pronounced ductal shunts without characteristic ductal murmurs, particularly within the first few days of life.[2 3] Clinical reference to 'opening of the duct' in preterm infants may be inaccurate: in most cases the duct will have been patent from birth and any increase in ductal shunt may be due to an increasing gradient between systemic and pulmonary pressures. The absolute values for ductal shunts measured in this study, however, even in the preterm group, are considerably smaller than those recorded in infants with ductal murmurs, wide pulse pressure, and incipient cardiac failure in the second and third weeks of life. The silence of early ductal shunts may be due to a combination of their small aortopulmonary gradients, their large calibre, and their small volume, which all contribute to a lack of turbulence.

We do not know how much clinical importance to attach to these early and usually small left to right ductal shunts. We speculate that during the early hours of life the sick or preterm infant may not be able to tolerate even an average shunt of 25% of left ventricular output because of the stressed and perhaps asphyxiated myocardium. If left ventricular output is not increased by an amount equalled by that of the ductal shunt then peripheral perfusion will be affected, especially that of the gastrointestinal tract, kidneys, and possibly that of the brain. At the same time the ductal shunt may exacerbate lack of compliance of lungs which are already atelectatic. Further study is required.

Interestingly, the size of ductal shunt measured at 48 hours was predictive of subsequent ductal murmurs. This suggests that many infants develop persistent ductal patency even at that early age. If this is so, Doppler ultrasound scanning might be used to select those infants who could benefit from pharmacological or other intervention to promote ductal closure. Again further study is required.

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# Effects of birth weight, gestational age, and maternal obstetric history on birth prevalence of cerebral palsy

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SUMMARY A register of children with cerebral palsy born to mothers resident in the Mersey region from 1966 to 1977 was compiled from health service records. Frequency distributions and prevalences of birth weight and gestational age differed for those with hemiplegia, diplegia, and quadriplegia. In particular, the children with diplegia showed a bimodal frequency distribution. Children of normal birth weight with diplegia had a higher prevalence of severe mental retardation than those of low birth weight. These differences may be due to survival bias and may not be of aetiological importance. Furthermore, the mothers of diplegic infants had a significantly higher proportion of spontaneous abortions, stillbirths, and low birthweight infants in their obstetric history. This suggests that prenatal factors predominate in the aetiology of diplegia.

The association between cerebral palsy and prematurity was first recognised in 1826, when Joerg noted that 'too early and unripe born fetuses may present a state of weakness and stiffness in the muscles persisting until puberty or later.[1] Subsequently Little in 1834 observed that contracture of the arms and legs occurred in premature infants[2] and later gave his classic description of cerebral palsy, in which the association with prematurity was again noted.[3]

More recently the association of cerebral palsy with retardation of intrauterine growth has been highlighted. Alberman showed in a case control study that birth weight was unduly low for gestational age in infants with spastic diplegia and quadriplegia and concluded that some prenatal factor was responsible.[4] McDonald, in a follow up of low birthweight infants, also found that birth weight and gestational age were independent risk factors for cerebral palsy,[5] an observation that was subsequently confirmed by both case control and longitudinal cohort studies.[6]

The bimodal frequency distribution of birth weight of infants with spastic diplegia was first recognised by Childs and Evans[7] and has been confirmed by others.[8–10] On the basis of this bimodality and the clinical differences between the two subgroups it was proposed that the aetiological factors leading to paraplegia and diplegia of low birthweight infants differed from those operating among infants of normal birth weight

The relevance of birth weight and gestational age as risk factors for cerebral palsy is assuming increasing importance with current trends in obstetric and neonatal management. These include the early recognition of growth retardation followed by induction of labour, and the technological developments in neonatal intensive care with the ability to keep progressively smaller infants alive. In the light of these developments we report the association between birth weight and gestational age in a geographically delineated cohort of patients with spastic cerebral palsy born from 1966 to 1977 and relate it to the observed prevalence of the syndrome

## Methods

A register was compiled of all patients with cerebral palsy born in the years 1966–77 whose mothers' area of residence at the time of birth was within the boundary of the Mersey Regional Health Authority. As the mother's area of residence was the criterion for inclusion infants born within the region but whose mothers' area of residence was outside were excluded, but those born outside whose mothers' area of residence was within the region were included. These inclusion and exclusion criteria were applied because denominator data for live births obtained from birth registration documents are published according to the mothers' area of residence at the time of birth.

The register was compiled from several sources, including the handicap registers of all health districts in the region, the national register of families claiming family disability allowance maintained by the Rowntree Trust in York, records of children attending schools for the educationally subnormal and the physically handicapped, and a search by the Office of Population Censuses and Surveys (OPCS) of all death certificates in which cerebral palsy featured as the underlying cause of death.

The type of cerebral palsy was categorised from information in the clinical records of each child. The notes of all doubtful cases were reviewed by one of us (LR). The spastic and mixed spastic syndromes provided the material on which this report is based. Patients with symmetrical or nearly symmetrical spasticity of the legs with lesser or no involvement of the arms were designated as having spastic diplegia Patients with unilateral spasticity of one arm or one leg, or both, were designated as having hemiplegia, and those whose arms and legs were equally affected, were designated as having spastic quadriplegia.

The mother's hospital obstetric record was used to obtain the child's birth weight. Denominator numbers of live births in the Mersey region for determining the prevalence of infants with cerebral palsy at birth were obtained from the Registrar General's and OPCS tables of birth registration. Grouped birthweight specific data for infants weighing 2500 g or less were obtained from the LHS 27/1 returns compiled by the Department of Health and Social Security (DHSS) from birth notifications. Numbers of live born infants weighing over 2500 g were obtained by subtracting notifications of births of 2500 g or less from total birth registrations.

To subdivide the denominator data for infants weighing over 2500 g into 500 g categories national data from England and Wales were used to obtain the proportion of infants in each category and these were applied to the total population of live births in the Mersey region to estimate the number of births in each birthweight category.[11]

Gestational age at birth was obtained from the hospital obstetric records for 540 cases in which the date of the last menstrual period was fairly certain. In an additional 51 cases an estimate of gestational age was found in the paediatric records. To obtain the denominator for the number of births in each gestational age group the proportions in each group in the 1970 British birth cohort were applied to all live births in the Mersey region.[12] Data from 1970 related to single births only. The 1970 cohort had to be used because there is no other routinely published source of data giving the frequency distribution for gestational age.

Appropriateness of birth weight for gestational age allowing for sex was determined by reference to standard charts giving third, 10th, and 50th centiles.[13] Data on the number of previous spontaneous abortions, stillbirths, live births, and infants weighing 2500 g or less were obtained from each mother's obstetric record.

Almost all the children were assessed by a clinical psychologist at least once, usually when school placement was being considered. Various assessment procedures were used. Where possible mental ability was classified according to intelligence quotient (IQ). Severe retardation was determined by an IQ of <50, moderate retardation by an IQ of 50–69, and normal or minimal retardation by an IQ of ≥70.

The significance of differences between proportions was calculated using $\chi^2$ low column analysis.

Table 1 *Type of spastic cerebral palsy classified by sex*

| | *No (%) with hemiplegia* | *No (%) with diplegia* | *No (%) with quadriplegia* |
|---|---|---|---|
| Male infants | 114 (58) | 81 (54) | 149 (60) |
| Female infants | 83 (42) | 68 (46) | 98 (40) |
| Total | 197 (100) | 149 (100) | 247 (100) |
| Male female ratio | 1 4 1 | 1 2 1 | 1 5 1 |

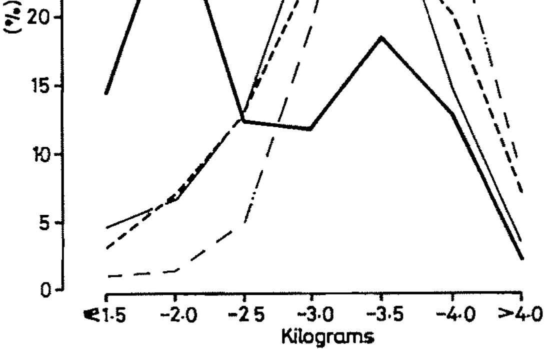

Fig 1 *Birthweight frequency distribution of cerebral palsy.*

## Results

The study population comprised 593 cases of spastic cerebral palsy. Table 1 shows the cases according to type of cerebral palsy and sex. There was a preponderance of male patients, and the three categories of syndrome showed similar male:female ratios.

### BIRTH WEIGHT AND SPASTIC CEREBRAL PALSY

Fig 1 shows the frequency distributions of birthweight for the three types of spastic cerebral palsy. Excluded from this analysis were five cases in whom there was no record of birth weight (two with diplegia and three with quadriplegia)

The hemiplegic and quadriplegic infants showed a unimodal distribution which was shifted to the left compared with the distribution of all live births in England and Wales. Those with diplegia showed a bimodal distribution with the major peak among the low birthweight infants. The differences in the frequency distribution of birth weight of the infants with spastic cerebral palsy were explained when the birthweight specific prevalences were examined (fig 2). (In this analysis the infants with cerebral palsy born in 1966 had to be excluded because denominator data on the numbers of live births in each birthweight category in the Mersey region were not available.) There was an exponential rise in the prevalence with decreasing birth weight in all three subgroups of spastic cerebral palsy, but the rise was most pronounced for those with diplegia. Thus the bimodality of the frequency distribution of birth weight in those with diplegia derived from a combination of the high rates among those of lower birth weight, even though the denominators were small, and the large numbers of births at the higher end of the birthweight frequency distribution.

### GESTATIONAL AGE AND SPASTIC CEREBRAL PALSY

In two cases (one of diplegia and one of quadriplegia) the gestational age was not recorded in either the maternal obstetric or the paediatric notes; the analysis was based on the remaining 591 cases.

The frequency distribution of gestational age was similar to that of birth weight for all three subgroups of spastic cerebral palsy, the diplegic infants again showing a bimodal distribution (fig 3). The gestational age specific prevalences increased with decreasing gestational age except among those whose gestational age was ≤28 weeks, where the prevalence was low (fig 4).

As with the frequency distribution of birth weight the bimodality of the gestational age curve for infants with diplegia was the consequence of the high prevalences among those infants whose gestational age was ≤36 weeks.

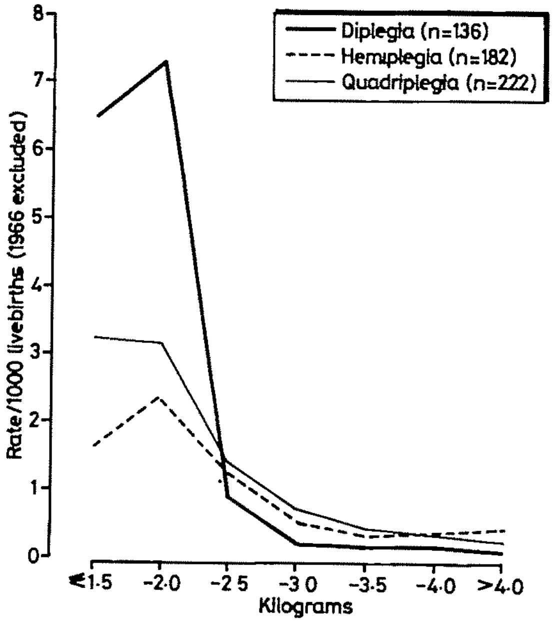

Fig 2 *Birthweight specific prevalence rates of cerebral palsy*

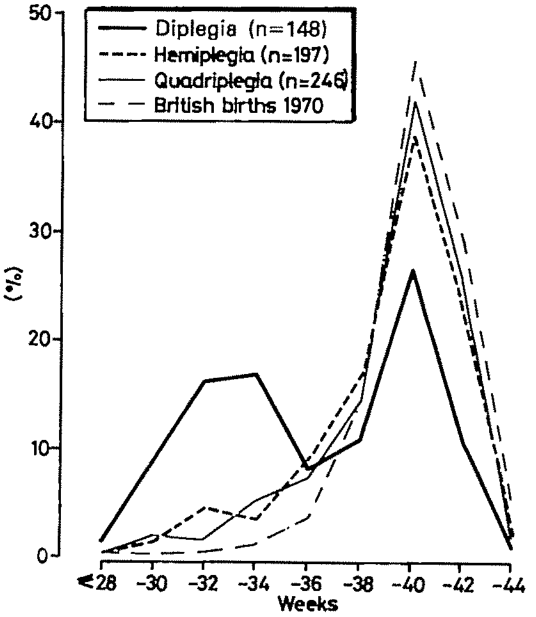

Fig 3 *Gestational age frequency distribution of cerebral palsy*

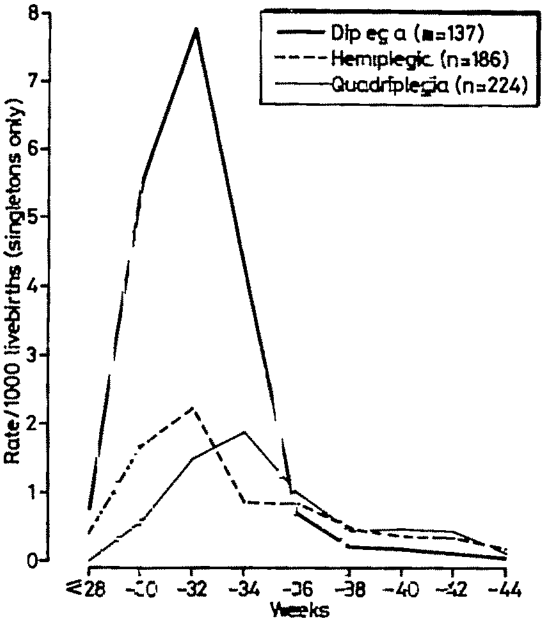

Fig 4 *Gestational age specific prevalence rates of cerebral palsy.*

Table 2 *Appropriateness of associating birth weight and gestational age. Values are numbers (%) of infants*

| *Centiles* | *Hemiplegia (n=197)* | *Diplegia (n=147)* | *Quadriplegia (n=244)* |
|---|---|---|---|
| <3rd centile | 22 (11·2) | 25 (17·0) | 39 (16·0) |
| <10th centile | 48 (24·4) | 50 (34·0) | 87 (35·7) |
| <50th centile | 130 (66·0) | 114 (77·6) | 157 (64·3) |

APPROPRIATENESS OF ASSOCIATIVE BIRTH WEIGHT AND GESTATIONAL AGE

Table 2 shows the proportions of cases falling below the third, 10th, and 50th centiles on the charts of birth weight for gestational age. The analysis concerns 588 cases in which both birth weight and gestational age were recorded. In all three categories of cerebral palsy a disproportionate number were small for gestational age; 11·2%, 17·0%, and 16·0% of those with hemiplegia, diplegia, and quadriplegia, respectively, fell below the third centile. A higher proportion of infants with diplegia seemed to have retarded growth at birth, while those with hemiplegia showed the least growth retardation, but these differences were not significant

MENTAL ABILITY AND BIRTH WEIGHT

There were 574 cases in which birth weight was known and a record of mental ability available. Table 3 shows mental ability in the three categories of cerebral palsy according to their birth weight groups. A greater proportion of those with quadriplegia showed severe mental retardation (64%, compared with only 24% and 13% among those with diplegia and hemiplegia, respectively).

In the very low birthweight group (≤1500 g), all three categories of cerebral palsy showed a greater proportion of infants with normal mental ability compared with the other birthweight groups (1501–2500 g and >2500 g).

MATERNAL OBSTETRIC HISTORY

All conceptions before the birth of each index case

Table 3 *Mental ability by type of cerebral palsy and birth weight (values are numbers (%) of infants)*

| *Birth weight and diagnosis* | *Mental ability* | | | *All* |
|---|---|---|---|---|
| | *Normal* | *Moderately retarded* | *Severely retarded* | |
| **≤1500 g** | | | | |
| Hemiplegia | 5 (83) | 1 (17) | 0 (0) | 6 |
| Diplegia | 16 (76) | 2 (10) | 3 (14) | 21 |
| Quadriplegia | 4 (40) | 4 (40) | 2 (20) | 10 |
| **1501–2500 g** | | | | |
| Hemiplegia | 27 (69) | 6 (15) | 6 (15) | 39 |
| Diplegia | 39 (65) | 10 (17) | 11 (18) | 60 |
| Quadriplegia | 10 (22) | 8 (17) | 28 (61) | 46 |
| **>2500 g** | | | | |
| Hemiplegia | 113 (74) | 19 (13) | 19 (13) | 151 |
| Diplegia | 33 (51) | 11 (17) | 21 (32) | 65 |
| Quadriplegia | 39 (22) | 19 (11) | 118 (67) | 176 |
| **Total** | | | | |
| Hemiplegia | 145 (74) | 26 (13) | 25 (13) | 196 |
| Diplegia | 88 (60) | 23 (16) | 35 (24) | 146 |
| Quadriplegia | 53 (23) | 31 (13) | 148 (64) | 232 |

Table 4 *Outcome of previous conceptions (Values are numbers (%) of infants)*

| | *Spontaneous abortions* | *Stillbirths* | *Low birthweight live births* | *Normal birthweight infants* | *Total conceptions* |
|---|---|---|---|---|---|
| Hemiplegia | 35 (14·0) | 2 (0·8) | 18 (7·2) | 195 (78·0) | 250 (100) |
| Diplegia | 55 (24·6) | 8 (3·6) | 23 (10·3) | 138 (61·6) | 224 (100) |
| Quadriplegia | 57 (12·6) | 14 (3·1) | 28 (6·2) | 353 (78·1) | 452 (100) |

were classified according to whether the outcome had been a spontaneous abortion, a stillbirth, a live birth weighing ≤2500 g, or a live birth weighing >2500 g. A summary of the outcomes of all previous conceptions according to type of cerebral palsy is shown in table 4. The difference was highly significant; in particular, the mothers of diplegic infants had had a greater proportion of spontaneous abortions, stillbirths, and low birthweight infants than the mothers of hemiplegic or quadriplegic infants ($\chi^2$=28·2, df 6, p=0·0001).

## Discussion

The bimodal frequency distribution of birth weight of the diplegic infants confirms previous observations.[7–10] The interpretation that this bimodality is the result of different aetiological factors, however, requires reassessment. In support of this thesis Childs and Evans noted that the proportion of severely mentally retarded infants was greater among infants of normal birth weight than among those with birth weights of <2500 g.[7] An alternative interpretation is that survival of infants in the two birthweight categories is biased according to the severity of brain damage, for which the marker is the degree of mental retardation. If this were so the low birthweight group would be less likely to show severe mental retardation because the most severely affected cases would have been aborted or died before the diplegia was recognised. In the normal birthweight group the severely mentally retarded have a better chance of survival because they do not have the additional hazard of prematurity. While the diplegic infants may not be a single entity, their aetiological subdivision cannot be justified on the basis of the bimodality of the birthweight distribution curve.

Another explanation of the higher proportion of severely mentally retarded among diplegic infants with normal birth weight could be that the longer the infant remains in a hostile intrauterine environment the greater the neurological deficit.

Drillien *et al* also noted differences between premature and mature cases in the mothers' social class distribution, age at marriage, and fertility pattern and concluded that these were attributable to differences in aetiology.[14] These results can, however, be explained by survival bias without invoking aetiological differences.

The survival bias is further evident on examination of the prevalences specific for gestational age. We have confirmed that infants with spastic cerebral palsy fail to grow normally in utero, with a disproportionate number, particularly of those with diplegia, being small for dates. Among infants with a very short gestational age (≤28 weeks) there is a sharp fall in the prevalence of cerebral palsy (fig 4). The sharp fall is likely to be an artefact of incomplete ascertainment because not only are the infants with cerebral palsy premature but their growth is retarded so that the chance of survival is severely compromised.

The bias introduced by differential survivals highlights the dangers inherent in advancing aetiological hypotheses on prevalence rather than incidence. In the current state of knowledge no study of cerebral palsy can provide data on incidence; at the very best only prevalence at birth can be determined because there is no method of ascertaining how many affected pregnancies are aborted or stillborn. Any factor that affects rates of abortion or stillbirth may also affect the prevalence of cerebral palsy at birth without being of aetiological importance. Even the ascertainment of prevalence at birth is incomplete because it is impossible to recognise all cases of cerebral palsy among those infants who die.

The higher proportions of spontaneous abortion, stillbirth, and low birthweight infants in the obstetric history of the mothers of diplegic infants lend support to the observation made by Dejerine that the aetiological factors leading to diplegia were prenatal in onset as opposed to those leading to hemiplegia, which were postnatal.[15] Freud, who first used the term cerebral diplegia, noted the difference in symptoms between that syndrome and hemiplegia; the former showed a diffuse bilateral symmetrical defect of the brain whereas the latter showed a gross lesion.[15] In this context infants with quadriplegia should be subdivided into those with diffuse lesions, and who can be classified with diplegic infants, and those who have double hemiplegia. If such a distinction cannot always be made on clinical examination, technological advances such as ultrasound scanning computed tomography or magnetic resonance imaging may help to delineate more precisely the epidemiology of the cerebral palsies and allow the formulation of specific aetiological hypotheses

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# Selective medical examinations on starting school

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SUMMARY Selective medical examination of children starting school has been operated in Cramlington for five years, and the data for the school year 1984–85 are reported. It is argued that the 'routine medical' is an outdated concept and that its abolition would allow more time for more important aspects of educational medicine including help for adolescents, disabled children in school, and deprived children who have not received basic health surveillance.

Since 1959 there has been no statutory obligation to carry out medical inspections of children at particular ages. Many local authorities became selective in their re-examination of children between 7 and 16 years but most retained the routine medical examination at school entry. This need has now also been questioned. The Court committee stressed the importance of observation by teachers and health visitors in the assessment of a child at school entry and felt that routine medical examinations failed to identify children's current problems.[1] Lowdon *et al*, in a study of 1255 routine school entry medical examinations, concluded that it would have been more profitable to coordinate information already available from the records of clinics and health visitors, and from class teachers, and hearing and vision screening, and thereby to select only a few children for formal examination.[2] Whitmore, in a study of 351 routine school entry medical examinations, concluded that there was a strong case not only for reducing the number of school entrants examined in some areas, but also for maintaining or improving the content and quality of the examinations of those selected.[3]

In 1978 a system of selective school entry medical examinations was introduced in Cramlington. We describe that system, report on the data for the school year 1984–85, and discuss why we believe a selective system should be used by more health authorities.

## Methods

Cramlington is a new town, started in 1965. It has a population of 26 000, of which 5000 are school children. It has a well circumscribed area in which family doctors operate from two health centres Most children are seen at the preschool clinics either by their family doctor or by a clinical medical officer. Doctors examined children aged 6 weeks, 2½ years, and 4 to 4½ years.

When a child starts school the parents are given a pamphlet explaining the school health service. During the first term all parents are sent a letter, which explains the system of selective school medical examinations and asks them whether they would like their child to see the school doctor.

If a child's immunisation record is unknown or not up to date the parents and the family doctor are informed. One year later the child's immunisation record on the health district computer is inspected to discover whether the omitted immunisations have been given. All children have their hearing and vision screened by technicians during their first year at school

When the child has been in school for a term a class review is arranged between the school doctor, reception teacher, school nurse and head teacher. This review takes about 45 minutes for 30 children The doctor brings to the review details of the preschool surveillance received by the child, and of identified medical problems. Any concern the teacher may have about a child can therefore be discussed in the light of medical information of which the school may have been unaware. Most children do not give cause for concern and the discussion can therefore concentrate on the few who do. The school then ensures that parents know of this concern and appropriate referral is made to—for example, the educational psychologist or speech therapist. Children on the non-accidental injury register are specifically discussed at the class review. Children are selected for medical examination only if there is: no preschool medical record; insuf-

Table *Reasons for selection for medical examination*

| *Reason* | *No of children* |
|---|---|
| Preschool records not available | 73 |
| No documentation of height heart, testes | 5 |
| Clarification of previously noted medical problems | 5 |
| Request by school | 7 |
| Request by parents | 5 |
| Total | 95 |

ficient detail in the record to be sure that height, heart, and testes have been checked; a need for clarification about a known medical condition or special educational need; the teacher has a worry about a child; or the parent has requested a consultation.

Between 20 and 30 minutes are allowed for each medical examination, and the results are discussed with teachers if parents are agreeable.

## Results

Ten primary schools in Cramlington had 494 entrants in the school year September 1984 to August 1985. Of these, 96 (19%) were selected to be seen by the school doctor. Most had a medical examination because their preschool record was not available, and in only one was a problem identified (enuresis). Twenty two children were seen for other reasons (table). Of the seven children reviewed at the request of their school, two were seen because of poor coordination and clumsiness; one because of delayed speech; one because of small stature; one for urinary frequency; two children were seen because they had a high rate of absenteeism. Of the five children seen at their parents' request, three required reassurance, one needed treatment for enuresis, and one child did not attend.

Twelve children and their parents did not attend their first appointment, but after two further invitations only two children had not been seen and their health visitors were informed.

## Discussion

This report describes one year of selective medical examinations carried out on school entry in Cramlington. The system has been running for five years, is no longer experimental, and is accepted by teachers and parents. We report it because 90% of health authorities continue to expect routine medical examinations for all children when they start school (CR Haines, personal communication) and we regard this as a poor use of time which could be better spent on other aspects of educational medicine.

The main argument against a routine system is that the organisation of medical care has changed and the important diseases which originally justified routine examinations are under control. Babies are now examined by doctors at birth; malnutrition is a rare problem; chronic infections such as tuberculosis are now uncommon; medical care is available free of charge to all preschool children and health visitors encourage the use of this service. Defects in vision and hearing are better identified by a screening service than as part of a medical examination. Educational psychologists now have the responsibility for assessing learning difficulties.

The new problems of childhood which have emerged and with which a school health service should be concerned are the effect of handicap on school life, the social, behavioural, and emotional difficulties of children, and language difficulties. These are precisely the problems which are difficult to assess at a medical examination, but which come to light at school, and which are best dealt with by close cooperation between doctors, teachers, and psychologists.

When the routine medical examination at school entry was a 'reasonable idea' and a 'reasonable use of resources', the burden of proof for its abolition rested with those who favoured such action. For the reasons already outlined, a selective system now seems to be the reasonable idea and reasonable use of resources, so the burden of proof for the retention of routine school medical examinations now rests with those who favour their retention. They must show that a routine medical examination will identify new problems which are amenable to treatment and which would not come to light in other ways. To our knowledge such proof is not available: indeed, the recent studies we know of suggest that identification of an important treatable condition at a routine medical examination is rare. A study of 124 such examinations by Polnay *et al* failed to identify any new conditions.[4] In Newcastle 40 children not selected for a medical were later examined as part of a research project and one new abnormality (an inguinal hernia) was found.[5]

An argument in favour of a routine system is that a neurodevelopmental examination can be performed. This takes various forms but usually concentrates on soft neurological signs such as clumsiness, mixed laterality, and choreiform movement. Such examinations are useful for research purposes but in our view should not be routine because the range of normal is not clearly defined, there is large interobserver variation; and children with learning, language, and behaviour difficulties are more likely to have minor neurodevelopmental abnormalities than controls. The reverse, however, is not true.[6] In addition, many minor neurodevelopmental problems improve spontaneously.[7] Learning and behaviour difficulties are not helped by treatment of an associated neurodevelopmental abnormality, and there are dangers in drawing to the attention of parents and teachers a problem of uncertain prognosis and importance which is unlikely to respond to treatment.

Although our report is from a new town, the Riverside Project in Newcastle showed that a similar system is practical in a deprived inner city area and argued that a selective system is even more important in such areas.[6] The need for doctors to support teachers is greater in inner cities as many parents do not attend routine medical examinations and do not see the relevance of the school health service. Resources in a selected system can be concentrated on the children who do not attend child health clinics, or about whom there is no record of screening and immunisation. These are the children about whom there should be concern

Whether a selective system saves time depends on how many selective medical examinations are needed after the class review. In the Riverside area, where the preschool services are underdeveloped and the population is mobile, 40% of children needed to be seen at school entry. No time was saved, but the time was used more profitably. In Cramlington only about 20% of children needed to be seen, so time was saved and was therefore available for other aspects of school health—notably, to help adolescents, disabled children in school, and deprived children who had not received basic health surveillance.

Most health authorities have already abandoned routine medical examinations after children have started school. Has not the time come for a similar change at school entry? Rather than wasting resources on routine activity, should not examination be directed to those children starting school who have not received the small number of important screening tests available and to those children about whom the teacher or parents are concerned?

We thank Dr John Tuke for many of the ideas in this article, and Mrs Joan Ryne for preparing the manuscript and for her efficient administration of the Cramlington school health service

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# Bone marrow transplantation in the treatment of α-mannosidosis

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SUMMARY Bone marrow transplantation was performed in a patient with α-mannosidosis. To our knowledge this is the first time such treatment has been attempted. The patient died 18 weeks after successful grafting and specimens of tissues were obtained at necropsy. Alpha-mannosidase activity in spleen and liver was just below normal (spleen 102 μmol/g/hour, control 113–330; liver 29 μmol/g/hour, control 30–131). Splenic α-mannosidase activity was indistinguishable from the control enzyme with respect to the Michaelis constant, heat stability, and inhibition by cobalt ions, as was 86% of the liver enzyme. In brain tissue α-mannosidase activity was 7% of controls, and less than one third had the properties of the normal enzyme. Oligosaccharides were present only in small amounts in liver and spleen, whereas they were greatly increased in brain tissue. Electron microscopic pictures of liver and spleen tissue showed normal morphology, but brain tissue showed definite vacuolation These findings suggest that transplantation reversed the somatic changes of α-mannosidosis but did not affect lysosomal storage within brain tissue. It is concluded that marrow transplantation may not be a suitable treatment for α-mannosidosis.

Bone marrow transplantation has been used to correct several inborn errors of metabolism by grafting donor leucocytes which synthesise the missing enzymes. Initial results in the mucopolysaccharidoses, Hurler's syndrome (mucopolysaccharidosis I) and Sanfilippo's syndrome (mucopolysaccharidosis III)[1] suggest that transplantation may be beneficial. In a recently reported case of infantile $G_{M1}$-gangliosidosis,[2] however, regression of hepatic and splenic enlargement without improvement of cerebral symptoms was described. We report a case of a child with α-mannosidosis (an oligosaccharidosis with many clinical similarities to Hurler's syndrome)[3] who received a bone marrow transplant, and we discuss the biochemical and electron microscopic findings in tissues removed at necropsy following his death 18 weeks after grafting.

## Case report

A 7 year old boy had typical clinical features of α-mannosidosis of facial dysmorphism, dysostosis multiplex, mental deficiency, deafness, hepatosplenomegaly, and recurrent infections.[3-6] The lymphocytes were vacuolated and IgG concentration was low at 3·56 g/l (normal 6·75–18·0). There were abnormal oligosaccharide bands in the urine and leucocyte α-mannosidase activity was grossly reduced at 2.9 μmol/g/hour (normal 250–1100 μmol/g/hour). In view of the recurrent infections and hepatosplenomegaly his prognosis was poor and he was unlikely to reach adult life.[6] For this reason and because reports of bone marrow transplantation in similar inherited disorders seemed encouraging,[1] bone marrow transplant was performed. The donor was the patient's 31 year old mother who had a one haplotype mismatch but who shared the same HLA DR type, and showed no reactivity on mixed lymphocyte culture.

Before operation the patient was given busulphan 2 mg/kg on four consecutive days followed by cyclophosphamide 60 mg/kg/day for four days. A dose of $3{\cdot}0\times10^8$/kg of cells was infused. Cyclosporin A was given as prophylaxis against graft versus host disease. Despite this he developed severe (grade III) acute graft versus host disease. Nine days after transplant he had generalised erythema, moderately severe diarrhoea, and raised liver enzyme activity with alanine transferase reaching 228 IU/l. He was given large doses of methyl prednisolone (1 g/m$^2$/

day on five consecutive days) and a suspected infection was aggressively treated with netilmicin 2·5 mg/kg, azlocillin 100 mg/kg, and metronidazole 10 mg/kg, each three times daily, and amphotericin 500 μg/kg once a day.

Four weeks after transplantation a bone marrow aspirate showed normal cellularity but reduced numbers of megakaryocytes. Chromosomal analysis of marrow cells showed a female karyotype in all 15 cells examined. Leucocyte α-mannosidase activity was normal at 406 μmol/g/hour and remained so until the patient's death. Free plasma α-mannosidase was recordable at 12 μmol/l/hour (normal 20–100 μmol/l/hour) and oligosacchariduria was considerably less than before grafting. The hepatosplenomegaly regressed to normal and vacuolated lymphocytes were no longer seen in the peripheral blood.

Over the next 12 weeks his progress was complicated by thrombocytopenia with recurrent bleeding and by neutropenia, lymphopenia, and hypogammaglobulinaemia, resulting in recurrent sepsis. Graft versus host disease of the skin became troublesome with a fluctuating maculopapular rash on limbs and trunk, and persistent erythema of the soles and palms. Attempts to control this by increasing doses of immunosuppressive drugs were associated with lymphopenia and a reduction in free plasma α-mannosidase (fig 1). This was reversed by withdrawal of all immunosuppressive drugs without progression of his skin rash.

He died from bronchopneumonia, 18 weeks after transplantation. Necropsy was carried out within six hours of death. *Candida albicans* was grown from the lungs although he had been treated with intravenous amphotericin for three weeks before death. Examination of marrow, which had shown a 46XX karyotype only 10 days before death, showed normal cellularity. There was no evidence of graft versus host disease except for the skin. Apart from the lungs, the only organ showing histological abnormality was the brain which showed focal haematoxyphil masses, probably due to calcification, and focal astrocyte gliosis in the white matter.

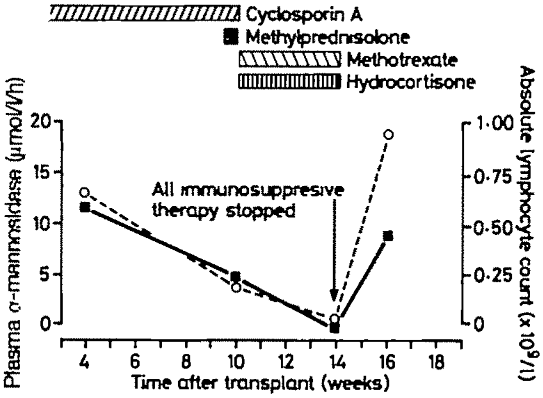

Fig 1 *Relation free enzyme activity in plasma, total lymphocyte, count, and immunosuppressive treatment·* ○- - -○ *lymphocyte count,* ■——■ *plasma α-mannosidase activity*

## Material and methods

### TISSUES

Samples of liver, spleen, and brain tissue were obtained at necropsy. Aliquots for electron microscopic examination were placed in 3% glutaraldehyde, the remainder being snap frozen in liquid nitrogen for biochemical studies and stored at −70°C until use. Samples from age matched controls were treated in an identical manner. All samples were obtained within six hours of death.

### OLIGOSACCHARIDE CHROMATOGRAPHY

Tissue samples were homogenised in water using an all glass homogeniser (Gallenkamp) and protein was precipitated by adding an equal volume of 5% (w/v) trichloroacetic acid. After centrifugation (4000 *g* for 30 minutes) aliquots of the supernatants equivalent to 5 mg of wet weight tissue were applied in 1 cm streaks to plastic backed silica gel chromatography plates (Whatman). Plates were developed, twice for 10 cm, in butanol/acetic acid/water (2/1/1; v/v/v). Carbohydrates were located using orcinol-sulphuric acid stain.[7]

### ENZYME STUDIES

Tissue samples were homogenised in 0·1% Triton X 100 at 4°C and sonicated on ice (Rapidis Model 50 ultrasonic disintegrator), at three bursts of 10 seconds at half power with 30 second intervals between bursts. After centrifugation (500 *g* for five minutes at 4°C) the supernatants were used for enzyme assay. Alpha-mannosidase activity was determined using 2 mM 4-methylumbelliferyl-α-D-mannopyranoside in 0·2 M sodium phosphate/0·1 M citric acid buffer, pH 4·0, as substrate

The assay contained 20 μl buffered substrate and sample (0·8–5·5 g protein/l) in a final volume of 40 μl. Incubation times were 15–60 minutes at 37°C. Reactions were terminated by adding 2 ml 0·5 M sodium bicarbonate sodium carbonate, pH 9·5, and the fluorescence produced was measured in an Aminco Bowman fluorocolorimeter (excitation 360 nm, emission 440 nm). Specific activities were calculated as μmol/g protein/hour. Protein concentrations were determined by the method of Lowry.[8]

The effect of cobalt ions was investigated by including 0–10 mM cobaltous sulphate in the standard assay.[6] Michaelis constant values were determined by Hanes plots using final substrate concentrations of 0 5–10 mM. For thermal stability studies, samples were diluted 9/1 (v/v) with 0·2 M sodium phosphate/0·1 M citric acid buffer, pH 6·0, heated at 60°C for up to 60 minutes, and cooled on ice before assay.

## Results

Thin layer chromatography of oligosaccharides extracted from tissues showed only slight increases in the liver and spleen of the patient compared with those of controls, but severely abnormal storage of oligosaccharides had persisted in the patient's brain (fig 2).

The table shows that almost normal amounts of acid α-mannosidase activity were present in the liver and spleen, but the activity in the brain was only 7% of the mean control value Acid α-mannosidase from the patient's spleen was stable to heating at 60°C, as was 86% of the activity in liver, but about 70% of the residual activity in the brain was heat labile (fig 3).

In all control tissues acid α-mannosidase activity was inhibited by cobalt ions. In the patient's tissues, activity in the spleen showed identical inhibition while that in the liver was only slightly inhibited and that in the brain showed about a threefold stimulation (fig 4). When these experiments were repeated after preincubating the tissue homogenates at 60°C for one hour, no difference in the effect of cobalt was found between the control and the patient's acid α-mannosidase activity in any tissue (fig 5).

Apparent Michaelis constant values determined by Hanes plots were measured for control enzyme and in patient's tissues both before and after heat inactivation at 60°C (table). The apparent Michaelis

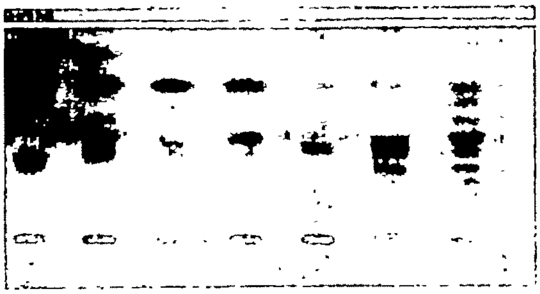

Fig 2 *Oligosaccharide chromatography of necropsy tissues (left to right, normal spleen, patient's spleen, normal liver, patient's liver, normal brain; patient's brain, and urine from patient before transplant*

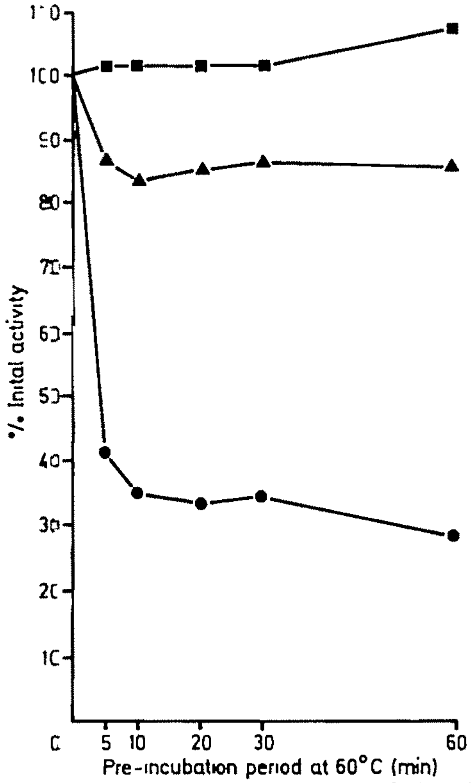

Fig 3 *Thermal stability of patient's brain ●, liver ▲, and spleen ■ α-mannosidase*

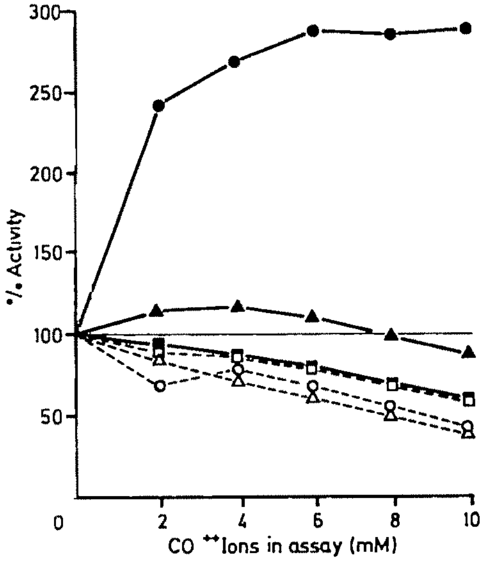

Fig 4 *Effect of cobalt ions on patient ——— and control – – – – α-mannosidase activity in brain ●, liver ▲, and spleen ■.*

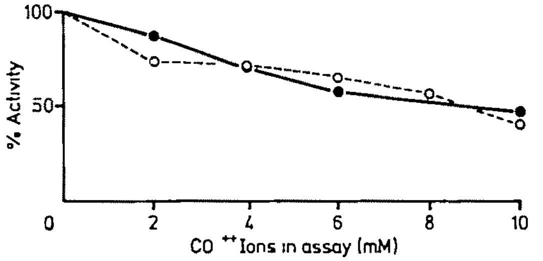

Fig 5 *Effect of cobalt ions on patient's brain ● and liver ○ α-mannosidase activity after preincubation at 60°C for one hour*

constant of the enzyme in the patient's splenic tissue was identical with control values, but the patient's liver and brain tissues before heat inactivation produced non-linear plots. Preincubating the tissues at 60°C produced values for the enzyme in patient's liver and brain identical with those from controls (table). Electron microscopy of liver (fig 6a)

Table *Alpha-mannosidase· specific activity and some properties of necropsy tissue*

| | *Specific activity (μmol/g/hour)* | *Michaelis constant (mM) before heating* | *Michaelis constant (mM) after heating** |
|---|---|---|---|
| Spleen | | | |
| Patient | 102 | 1 0 | 1 0 |
| Controls (n=3) | | | |
| Range | 113–330<br>(mean 194 76) | 0 9–1 0 | 0 9–1·0 |
| Liver | | | |
| Patient | 29 | Non-linear | 1 0 |
| Controls (n=3) | | | |
| Range | 30–131<br>(mean 53 6) | 0 8–1·0 | 0·8–1·0 |
| Brain. | | | |
| Patient | 3 1 | Non-linear | 1·0 |
| Controls (n=3) | | | |
| Range | 21–65<br>(mean 43·7) | 0·9–1·0 | 0 7–0 9 |

*For 60 minutes at 60°C

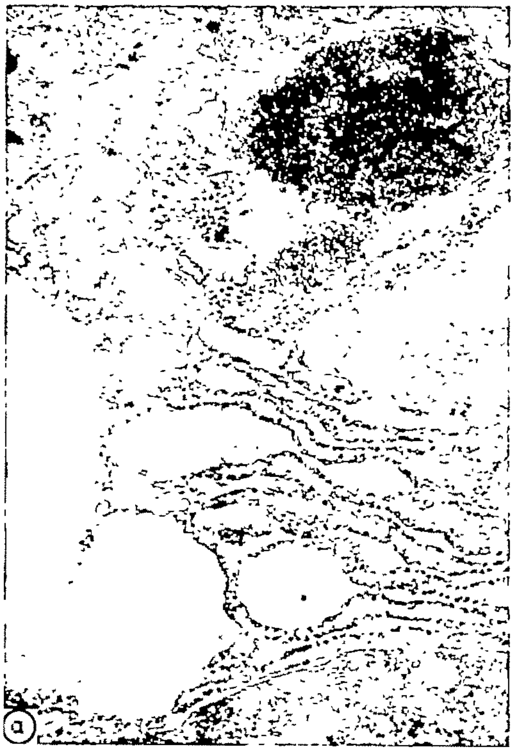

Fig 6a *Electron micrograph of liver 18 weeks after transplant showing normal morphology*

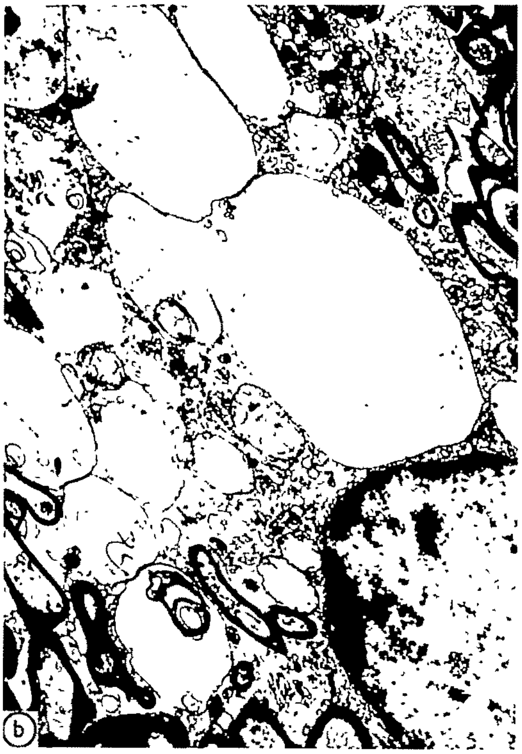

Fig 6b *Electron micrograph of brain 18 weeks after transplant showing pronounced cytoplasmic vacuolation.*

showed normal morphology in contrast to the pronounced cytoplasmic vacuolation reported in untreated patients with α-mannosidosis.[9] The brain, however, showed extensive vacuolation of the cytoplasm (fig 6b), suggesting little or no degradation of the mannose rich oligosaccharides stored within its lysosomes.

## Discussion

Acid α-mannosidase activity has three properties which allow normal and mutant α-mannosidosis enzymes to be distinguished. Normal enzyme is heat stable at 60°C, while mutant enzyme is rapidly inactivated at this temperature.[10] Cobalt ions inhibit normal acid α-mannosidase activity but stimulate residual mutant enzyme.[6] The mutant acid α-mannosidase activity has a much higher Michaelis constant than normal enzyme.[6]

Acid α-mannosidase activity of the patient's spleen was indistinguishable from the control enzyme with respect to heat stability (fig 3), inhibition by cobalt ions (fig 4), and Michaelis constant (table). This is to be expected because of the concentration of white cells in this organ. The white cell population was shown consistently to originate from the donor by its female karyotype. The slightly reduced specific activity of acid α-mannosidase compared with control values (table) probably reflected the carrier state of the bone marrow donor.

The near normal acid α-mannosidase activity in the patient's liver was probably due to a mixture of abnormal α-mannosidosis enzyme and normal enzyme transferred from donor white cells. This was shown by: the partial instability to heating (fig 3) (the mutant enzyme being heat labile at 60°C); the reduced inhibition by cobalt ions (fig 4) due to stimulation of the mutant enzyme by cobalt ions; and the anomalous Hanes plots due to the differing Michaelis constant values of the normal and mutant enzymes. After destruction of the mutant enzyme component by heating, a normal Michaelis constant value of 1 mM (table) and inhibition by cobalt ions similar to controls were shown (fig 5). Of the total acid α-mannosidase activity, 86% was normal enzyme contributed by donor cells, shown by its thermal stability (fig 3). Some of this activity was attributable to white cells in vessels within the liver. The regression of hepatomegaly, absence of cytoplasmic vacuolation (fig 6a), and the presence of only residual amounts of abnormal oligosaccharides (fig 2) strongly suggested that normal acid α-mannosidase had been transferred to hepatic lysosomes, facilitating degradation of stored mannose rich oligosaccharides within the lysosomes. Similar clinical regression of somatic abnormalities has been reported in other lysosomal storage diseases after bone marrow transplantation.[1 2]

In patients with α-mannosidosis the brain may contain up to 21% of the mean control α-mannosidase activity.[3] In our patient the enzyme activity in the brain was 7% of the mean control value (table). Less than one third had the properties of normal enzyme with respect to heat stability (fig 3), inhibition by cobalt ions (figs 4 and 5), and Michaelis constant (table). It is not possible to say whether the small amount of normal enzyme was already present before bone marrow transplantation, but no residual activity with the properties of normal enzyme was seen in cultured skin fibroblasts. Thus the normal acid α-mannosidase activity of the patient's brain, possibly contributed by donor cells, was only about 2% of the mean control values. At least part of this residual activity must have been due to white cells within vessels in the brain. Indeed, the persistence of cytoplasmic vacuolation (fig 6b) and grossly abnormal oligosaccharide storage within brain tissue (fig 2) suggest that little if any normal acid α-mannosidase had crossed the blood brain barrier and entered lysosomes within the brain cells.

These results correlate well with the case of a chimeric Angus calf with α-mannosidosis.[11] The calf, which exhibited male phenotype, obtained a natural transplant of lymphocytes from its normal female twin during fetal development as a result of placental fusion. Chromosome analysis of 200 lymphocytes showed two cell populations, 77% 60XX and 23% 60XY, indicating 77% of lymphocytes were 'donor' in origin. At necropsy, performed at the age of 14 months, liver, pancreas, and lymph nodes were less affected than those of a control group of animals with α-mannosidosis, but the brain was histologically similar to that of affected animals.

Several animal models of lysosomal storage diseases have been identified and central nervous system changes evaluated after bone marrow transplantation. Considerable α-fucosidase activity was recently shown in the brains of dogs affected by canine fucosidosis following transplant, and central nervous system lesions were reversed.[12] In other animal models—for example, sphingomyelinase deficiency[13] and β-glucuronidase deficiency[14] of mice and aryl sulphatase B deficiency of cats[15]—no transfer of enzyme to brain was seen. This suggests that there are differences in the amounts of enzyme which cross the blood brain barrier. In those disorders in which transfer of minute amounts of enzyme takes place it is doubtful whether any functionally beneficial effect on the brain can be expected.

In the one reported case of bone marrow transplantation in a patient with metachromatic leucodystrophy the white cells in the cerebrospinal fluid were shown to originate from the donor's grafted bone marrow.[16] This finding should be interpreted with caution. As the bone marrow is the main source of white cells in the cerebrospinal fluid, their presence in that fluid is to be expected, but it would be misleading to conclude that the enzyme has actually crossed the blood brain barrier and entered the brain tissue. A progress report on this patient's neurological state and mental development is required.

It has been argued that bone marrow transplantation should be performed as soon as possible after birth if maximum benefit is to be obtained,[17] but this depends on the amount of enzyme transferred into the brain. Although our patient did not have a transplant until the age of 6 years, the quantity of normal α-mannosidase transferred was extremely small. Whether more prolonged survival of the present case would have changed the biochemical findings in the brain and produced any functional benefit is open to speculation. We think that this is unlikely as clinical, biochemical, and electron microscopic changes in the liver and spleen were extremely rapid From our results we conclude that bone marrow transplantation may not affect the neurological course of patients with α-mannosidosis. It is also possible that other lysosomal storage disease affecting the central nervous system (such as some mucopolysaccharidoses) may not respond to this form of treatment.[12] It is therefore important that if such patients die after bone marrow transplantation every effort should be made to undertake the type of studies we have described, so that the results of treatment can be quantitated precisely.

We thank members of the nursing staff of the bone marrow unit for their devoted attention to this patient We also thank Professor B Marsden for his help in interpreting the electron micrographs

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## *Special report*

# Mental development in congenital hypothyroidism after neonatal screening

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In 1961 at the International Congress of Mental Retardation in Vienna the late Henning Andersen, one of the founder members of the European Society for Paediatric Endocrinology (ESPE), emphasised the importance of early treatment of children with congenital hypothyroidism and hoped that methods would soon be available to allow the diagnosis to be made soon after birth.[1] At the annual meeting of ESPE in 1974 Pierre Rochiccioli[2] was the first in Europe to report such a method, and in 1978 and 1979 reports on national[3–5] and regional neonatal screening programmes[6–8] for diagnosing congenital hypothyroidism were presented. These activities prompted the ESPE to start collaborative studies on congenital hypothyroidism.

A working party was established consisting of three ESPE members assisted by experts in the special problems to be studied. To facilitate international collaboration one representative from each country was appointed. The tasks of the working party comprised making recommendations on technical problems, organising follow up of patients, writing regular progress reports, and carrying out collaborative studies. Information was exchanged by letters, questionnaires, and progress reports sent to all members of ESPE and others participating in neonatal thyroid screening.

This paper gives the results of a collaborative study on mental development in children with congenital hypothyroidism diagnosed by neonatal thyroid screening[9] and the latest progress report on how screening programmes are being developed in Europe.

Children with congenital hypothyroidism are heterogeneous with regard to various factors that may influence mental development. Some are related to congenital hypothyroidism—for example, athyroidism, ectopic thyroid gland, dyshormonogenesis, prenatal onset of hypothyroidism, and age at start of treatment—while others are not—for example, complications of pregnancy and delivery, associated disorders, congenital malformations, and the socioeconomic state of the family.

As a result of the collaboration of paediatricians and psychologists from 14 European countries we were able to analyse the importance of some of these factors in the mental development of a large number of children with congenital hypothyroidism. Two questionnaires were sent out: one asked for data on individual children with congenital hypothyroidism, the other concerned the reference or control values for the respective developmental and intelligence tests used in the different centres.

Initially we planned to express the results of developmental and intelligence tests (DQ, IQ) as a standard deviation score, a method that would have enabled us to pool results of different tests and age groups. Unfortunately, this plan had to be abandoned because the relevant reference values necessary were not available or did not represent unselected population samples. The results are therefore expressed as absolute figures for age and test methods separately. Statistical analyses were carried out with the Mann-Whitney and Kruskal-Wallis tests.

## Results

A total of 928 questionnaires on children with congenital hypothyroidism were obtained; 138 could not be analysed, however, because answers were incomplete or sample numbers per test were too small for statistical evaluation, or both. The following analysis is therefore based on data on 790 children who underwent a total of 1590 tests. Table 1 shows the aetiology of the congenital hypothyroidism and the age of the children at the start of treatment. There were 571 girls and 216 boys; the sex of three of the children was not specified. One hundred and forty seven had had complications during pregnancy or delivery, and 71 had associated

Table 1 *Aetiology of congenital hypothyroidism and ages at start of treatment*

| *Aetiology* | *No of children* | *Age at start of treatment (days)* | *No of children* |
|---|---|---|---|
| Athyroidism | 221 | 1–15 | 212 |
| Ectopic thyroid | 343 | 16–30 | 333 |
| Dyshormonogenesis | 81 | 31–45 | 146 |
| Other | 20 | 46–60 | 40 |
| Unknown | 125 | 61–90 | 27 |
| | | 91 and over | 18 |

illnesses or malformations. The socioeconomic state of the family as judged by paternal occupation and maternal education was high in 172, middle in 394, and low in 162; in 62 it was not known. In 46 children socioemotional conditions were considered to be inadequate.

The screening programme was successful in that thyroid substitution was initiated in 545 infants (69%) before the age of 1 month. In the remaining children, however, treatment was delayed, sometimes for more than 90 days, which is unacceptable for a neonatal screening programme unless treatment was postponed intentionally: in some newborn infants with raised serum concentrations of thyroid stimulating hormone, concentrations of thyroxine were normal in the beginning. Repeated estimations at intervals of two weeks showed, however, a decline in thyroxine concentration and a rise in thyroid stimulating hormone concentration, indicating the necessity for thyroxine replacement, usually at the age of 2–4 months.

Table 2 shows the results of the developmental and intelligence tests applied at different ages. They are all generally accepted methods of evaluating mental development in infants and children. The numbers tested decreased with age because neonatal thyroid screening was introduced only during recent years. For the same reason the number of children tested in many of the participating centres over the age of 5 years was relatively small for statistical evaluation.

Fig 1 is a summary of DQ and IQ results grouped according to age and test methods. In an attempt to show the influence of risk factors and associated findings on mental development simultaneously, the results are given as means (SD) in four columns showing the total number of children with congenital hypothyroidism, the number with additional risk factors, the number with associated diseases or malformations, and the number without other findings. Mean DQ and IQ scores were within the normal ranges in most age and test groups. Risk factors and other diseases were associated with lower mean scores. Conversely, children without risk factors or other diseases tended to have higher mean scores. This pattern was seen in most age groups and test methods with sufficient sample sizes.

Interestingly DQ and IQ scores obtained with different test methods at certain ages showed large variations. As these tests were carried out in various centres we do not know whether the variations are due to different handling of the test methods or differences in the populations tested, or are inherent in the test methods themselves. This merits further study.

The influence of the socioeconomic state of the

Table 2 *Methods of testing development and intelligence in 790 children at different ages*

| *Method* | *Age at testing (years)* | | | | | | | | | *Total No* |
|---|---|---|---|---|---|---|---|---|---|---|
| | *6 months* | *1* | *1½* | *2* | *3* | *4* | *5* | *6* | *7* | |
| Brunet-Lezine | 99 | 253 | 75 | 162 | 64 | 15 | 4 | | | 672 |
| Griffiths | 64 | 152 | 70 | 95 | 66 | 42 | 16 | | | 505 |
| Bailey | | 26 | 19 | 118 | 10 | | | | | 173 |
| Stanford-Binet | | | | 2 | 30 | 15 | 10 | 1 | 1 | 59 |
| Terman-Merrill | | | | 18 | 12 | 26 | 2 | | | 58 |
| Snijders-Oomen | | | | | | 31 | | 1 | | 32 |
| WPPSI | | | | | | 1 | 23 | 1 | | 25 |
| WISC | | | | | | | | 14 | 3 | 17 |
| Kramer | | | | | 4 | 8 | | 4 | | 16 |
| HAWIVA | | | | | | | | 2 | 13 | 15 |
| Gesell | | 7 | 2 | | 1 | | | | | 10 |
| NEMI | | | | | | | 5 | 3 | | 8 |
| Total | 163 | 438 | 166 | 395 | 187 | 138 | 60 | 26 | 17 | 1590 |

WPPSI=Wechsler preschool and primary scale of intelligence, WISC=Wechsler intelligence scale for children, HAWIVA=German version of WPPSI, NEMI=Nouvelle echelle métrique de l'intelligence

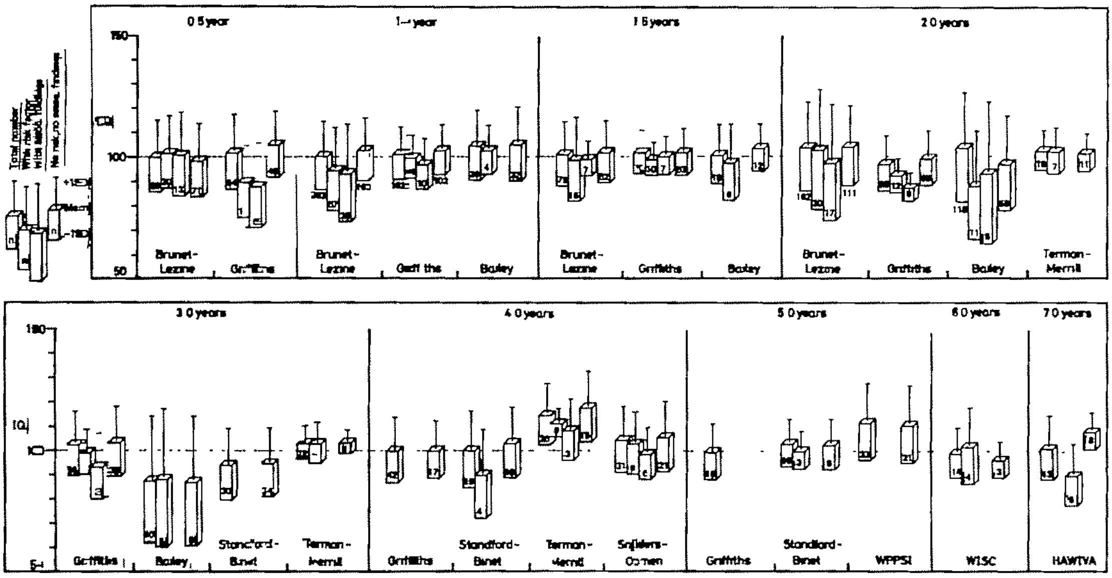

Fig 1 *Developmental and intelligence quotients in 790 children with congenital hypothyroidism. Results are grouped according to age and test methods.*

family, classified as high, middle, and low, was tested by the Kruskal-Wallis analysis of variance. Table 3 shows that differences between the three classes were not (or weakly) significant in infants up to 1 year of age. There was, however, a significant increase in impact on mental development with increasing age.

Among the factors directly related to congenital hypothyroidism that may influence mental development we have studied aetiology and delay in starting treatment. We found that athyroid children had lower IQ and DQ scores than those with ectopic thyroid glands in 19 of 21 test groups. Table 4, however, shows that these differences were significant in only five groups. Hence, the aetiology of hypothyroidism seems to play a minor part in mental development.

In many of the athyroid infants treatment was started relatively late. It seems that the length of time for which they were completely deprived of thyroid hormones after birth was the predominant factor. We tested this assumption by correlating the age at the start of treatment with the results of developmental testing. To exclude the influence of other factors this analysis was carried out in athyroid infants without perinatal risks or associated findings. Fig 2 shows this correlation in athyroid infants at the age of 1 year, the only age group large enough for statistical analysis. As these 116 children were tested in different centres and by different test methods absolute figures could not be used for this evaluation. Individual results were therefore expressed in terms of the standard deviation score devised from the mean and SD of each child's own test group. Fig 2 shows that there was a significant negative correlation between mental development and the age at the start of treatment. DQ scores of infants for whom thyroid substitution had been started during the first month of age showed a more or less

Table 3 *Influence of socioeconomic state of family on mental development*

| *Age (years)* | *Test method* | *No** | *Analysis of variance (p value)* |
|---|---|---|---|
| 6 months | Brunet-Lezine | 99 | NS |
| | Griffiths | 64 | NS |
| 1 | Brunet-Lezine | 253 | NS |
| | Griffiths | 152 | <0·05 |
| | Bailey | 26 | NS |
| 1½ | Brunet-Lezine | 75 | <0·005 |
| | Griffiths | 70 | <0·01 |
| 2 | Brunet-Lezine | 162 | <0·01 |
| | Griffiths | 95 | <0·01 |
| | Bailey | 118 | <0·001 |
| 3 | Griffiths | 66 | <0·01 |
| | Stanford-Binet | 30 | NS |
| 4 | Griffiths | 42 | NS |
| | Terman-Merrill | 26 | <0·005 |
| | Snijders-Oomen | 31 | <0·025 |
| 5 | Griffiths | 16 | <0·05 |

*Test groups with n<4 were excluded

Table 4 *Influence of aetiology on mental development analysed by difference in DQ or IQ scores between patients with athyroidism and those with ectopic thyroid glands*

| *Age (years)* | *Test method* | *No tested* | *Difference in DQ (p value)* | *Age (years)* | *Test method* | *No tested* | *Difference in IQ (p value)* |
|---|---|---|---|---|---|---|---|
| 6 months | Brunet-Lezine | 99 | <0 001 | 3 | Griffiths | 66 | NS |
| | Griffiths | 64 | 0 023 | | Stanford-Binet | 30 | NS |
| 1 | Brunet-Lezine | 253 | <0 001 | 4 | Griffiths | 42 | NS |
| | Griffiths | 152 | NS | | Terman-Merrill | 26 | NS |
| | Bailey | 26 | NS | | Snijders-Oomen | 31 | NS |
| | Gesell | 7 | NS | | | | |
| 1½ | Brunet-Lezine | 75 | 0-046 | 5 | Griffiths | 16 | NS |
| | Griffiths | 70 | NS | | WPPSI | 23 | NS |
| | Bailey | 19 | NS | | | | |
| 2 | Brunet-Lezine | 162 | <0 001 | 6 | WISC | 14 | NS |
| | Griffiths | 95 | NS | 7 | HAWIVA | 13 | NS |
| | Bailey | 118 | NS | | | | |

normal distribution, whereas DQ scores of children treated later than 50 days of age were all below the normal mean. These results underline the importance of starting thyroid replacement treatment as early as possible.

## Conclusion

The aim of neonatal thyroid screening is to prevent mental retardation by diagnosing hypothyroidism early and starting thyroid replacement treatment as soon as possible. With fairly simple and inexpensive means it should be possible to shift the distribution curves of DQ and IQ that were found in hypothyroid patients before screening started towards those of healthy children (fig 3). The results of our collaborative study show that we are approaching this aim. This study also shows that risk factors and other diseases may also have a considerable influence on mental development and should not therefore be neglected in such an investigation.

In response to our inquiry in 1985 we received detailed data on the mental development of nearly 1000 individual patients with congenital hypothyroidism, which represents about 14% of all children with congenital hypothyroidism detected in Europe since the introduction of neonatal thyroid screening.

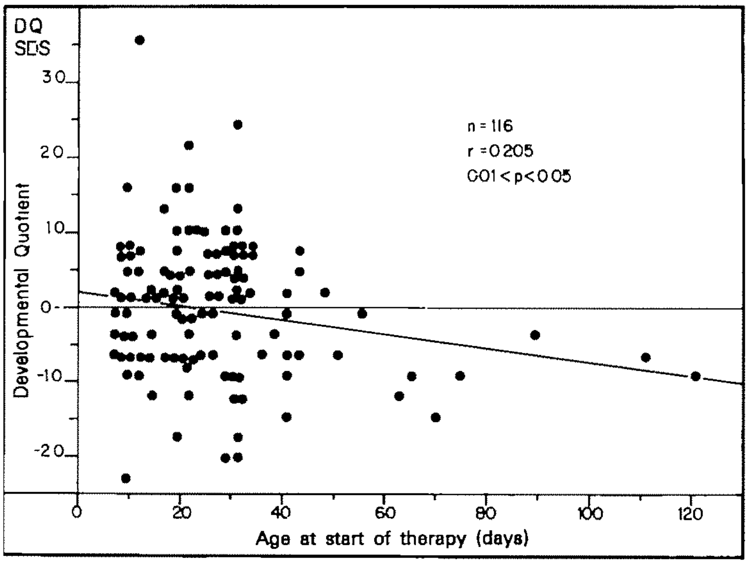

Fig 2 *Influence of age at start of treatment on mental development: correlation tested in athyroid infants without risk factors or associated findings at age of 1 year*

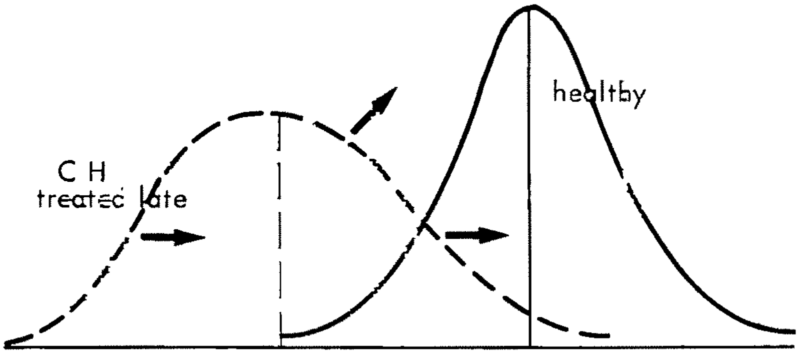

Fig 3 *Distribution of DQ and IQ scores in children with congenital hypothyroidism before introduction of neonatal thyroid screening (left) and in healthy children (right); arrows indicate shift of mental outcome towards normal*

Table 5 *Progress report: neonatal thyroid screening in Europe based on inquiries of ESPE working group on congenital hypothyroidism*

| *Year* | *No of infants screened* | *Increase per year* | *No of cases detected* | *Incidence of congenital hypothyroidism* |
|---|---|---|---|---|
| 1979 | 1 501 180 | +1 033 320 | 429 | 1 3500 |
| 1980 | 2 534 500 | + 750 100 | 744 | 1 3400 |
| 1981 | 3 284 600 | + 468 670 | 951 | 1.3500 |
| 1982 | 3 753 270 | + 269 841 | 1064 | 1 3500 |
| 1983 | 3 923 111 | | 1250 | 1 3150 |
| 1984 | * | + 244 385‡ | | |
| 1985 | 4 411 880† | | 1273† | 1 3450 |
| 1975–85 | 24 743 133† | | 6518† | 1 3800 |

*No separate data collection from 1975 to 1978 and in 1984, †total No recorded in February 1986, ‡mean increase

This shows that in many screening centres many children have not only been diagnosed and treated but also followed up carefully.

## Progress report

Table 5 shows the results of the latest inquiry in January–February 1986. During 1985, 4 400 000 newborn infants were screened in Europe and 1273 children with congenital hypothyroidism were diagnosed. Since 1975, the beginning of neonatal thyroid screening in Europe, nearly 25 000 000 infants have been tested and 6500 children with congenital hypothyroidism have been diagnosed, an incidence of one in about 3800 newborn children. After an early rapid increase in the number of infants being screened each year the rate is now stabilising as screening programmes have been widely introduced. National screening programmes covering over 90% of neonates have been introduced in Austria Belgium, Denmark, Finland, France, Federal Republic of Germany, Greece, Hungary, Iceland, Ireland, Israel, Luxembourg, The Netherlands, Norway, Spain Sweden, Switzerland, and the United Kingdom; programmes covering 50–75% of neonates have been introduced in Czechoslovakia, Italy Portugal, and Yugoslavia; and programmes covering 10–20% of neonates have been introduced in the Democratic Republic of Germany and Poland. This is indeed a great success considering that neonatal thyroid screening was first introduced only 10 years ago.

Data on mental development in children with congenital hypothyroidism were obtained from the following physicians and psychologists (listed in alphabetical order according to countries and cities): Belgium: M Verboven (Brussels), R Wolter (Brussels), M Vanderschueren-Lodeweyckx (Leuven), JP Bourguignon (Liège), P Malvaux (Louvain). Denmark: B Brock-Jacobsen (Roskilde/Copenhagen) England DB Grant (London) Federal Republic of Germany: A Grueters (Berlin), M Klett (Heidelberg). Finland. M Virtanen (Helsinki) France JP Farriaux (Lille), M David (Lyon), JE Toublanc (Paris), P Rochiccioli (Toulouse) Greece S Pantelakis (Athens) Israel J Sack (Tel Hashomer) Italy E Cacciari (Bologna), C Romano (Genova), G Chiumello (Milan), G Giovannelli, C Volta (Parma), L Moschini (Rome), GC Mussa (Turin), D Gaburro (Verona) Netherlands A Kalverboer (Groningen). Norway S Heyerdahl (Oslo) Scotland HJ Jackson (Glasgow) Sweden A Ilicki, A Larsson (Uppsala) Switzerland: K Zuppinger (Berne), P Sizonenko (Geneva), R Illig (Zurich).

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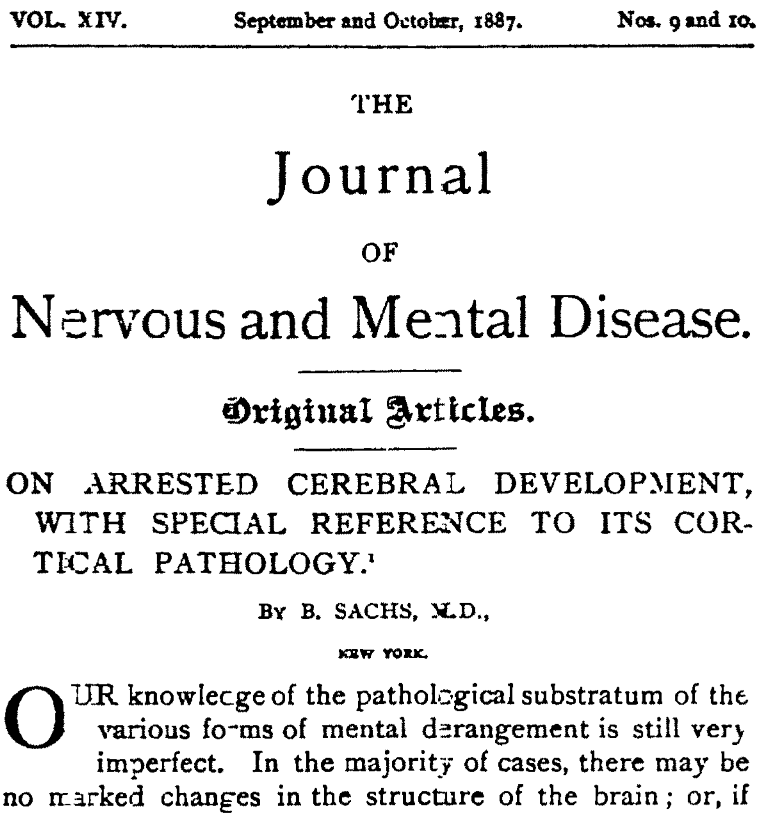
*Archives of Disease in Childhood*, 1987, **62**, 1056–1059

***Historical article***

# Tay-Sachs disease: a centenary

F R EVANS



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THE

## Journal

OF

## Nervous and Mental Disease.

**Original Articles.**

### ON ARRESTED CEREBRAL DEVELOPMENT, WITH SPECIAL REFERENCE TO ITS CORTICAL PATHOLOGY.[1]

BY B. SACHS, M.D.,

NEW YORK.

OUR knowledge of the pathological substratum of the various forms of mental derangement is still very imperfect. In the majority of cases, there may be no marked changes in the structure of the brain; or, if

One hundred years ago Sachs[1] published in great detail the clinical features, diagnostic signs, and pathology of a patient with a 'new' condition which, with that of Warren Tay,[2] was to bear his name. Sachs did not know in 1887 that Tay had forestalled him

In 1881 Tay (1843–1927) described the case of a 12 month old infant who from the age of 2 or 3 weeks had increasing weakness of the neck and limbs. Of the optic fundi he wrote; 'in the region of the yellow spot in each eye there was a conspicuous tolerably defined large white patch, more or less circular in outline, and showing at its centre a brownish red, fairly circular spot . which seemed to be a gap in the white patch through which one saw healthy structure.' This is well shown in the colour plate accompanying the case report. Tay called in his two colleagues Jonathan Hutchinson (1828–1913) of the eponymous teeth and Hughlings Jackson (1835–1911) of epilepsy fame The great neurologist could throw no further light on the case, saying there seemed no evidence of cerebral affection to account for the weakness. Six months later at post mortem examination the sole cerebral abnormality noticed was a large cavity containing old blood clot outside the left lateral ventricle.[2]

Warren Tay, a general surgeon, ophthalmologist, and dermatologist, was 'an untiring hospital officer . . . adding the subject of pediatrics at the Hospital for Children Hackney Road. . . . He was a walking dictionary at the London Hospital in the nineties,'[3] and 'would suffer even fools gladly.'[4]

Bernard Sachs (1858–1944) was a different sort of man, outgoing, humorous, and widely known. He was president of the New York Academy of Medicine and in 1931 president of the First International Congress of Neurology in Berne. He wrote nearly 200 papers and a text book. His parents were said to have eloped from Bavaria to Baltimore where Bernard was born. Although he maintained his German contacts, he was American in mind and preferred to be called Barney.[5]

After four years at Harvard he entered the medical school at Strasbourg, a recent German conquest, at a time when the Johns Hopkins, Cornell, and New York medical schools did not exist. He went on to study under Charcot in Paris, eventually becoming professor of neurology at the New York Polyclinic and attending physician at Mount Sinai, Montefiore, and Bellevue Hospitals.

In July 1887 he presented his paper on 'arrested cerebral development' before the American Neurological Association. It was published in October the same year and described the progressive condition from the age of 2 to 3 months, until death at the age of 2 years, of a girl whose mother had been thrown out of a carriage when five months pregnant. The child's progressive weakness gave normal muscular response to galvanic and faradic stimulation. The decreasing intellectual process was accompanied by loss of vision, but not of hearing. As Sachs wrote, 'The slightest touch and every sound were apt to startle the child.'

Neither Tay nor Sachs coined the famous phrase 'cherry red spot', but Sachs quoted the report of the New York and Berlin ophthalmologist Herman Joseph Knapp (1831–1911)· 'Child two to three months; nystagmus vibratorius . . . Fovea centralis of a cherry red colour surrounded by an intense greyish white opacity.' Knapp is said to have reported his findings at the 17th meeting of the Heidelberg Ophthalmological Society, as published in the proceedings of that meeting, but I have been unable to trace this.

When Knapp saw the child again at 1 year and ten months she was totally blind with complete optic atrophy: 'disc as white as paper with scarcely any trace of blood vessels Maculea lutea essentially as before' (It is doubtful if neurologists used ophthalmoscopes at that time. The electric ophthalmoscope was invented later by Charles Henry May (1861–1943) of New York.) The patient's eyes were not examined after death, but the optic nerves were variously stained and found to be normal. 'Blindness must therefore have been due either to the retinal changes or to the deficient cortical condition, or to both'.[1] Sachs noted that similar fundal appearances had been reported by Magnus and by Goldzieher, but without explanation. According to Sachs, their reports appeared in 1855

Sachs's own account is distinguished by careful pathology with detailed descriptions of convolutions and sulci, and there is a striking photograph of the brain after fixation. Blocks were made from six sites on each cerebral cortex, and sections cut from all except the cuneus which was too brittle, although paraffin and celloidin embedding were already in use at that time.[6] Pronounced changes in shape, axis, nuclei and nucleoli were found in the small and large pyramidal cells, with hardly any of a normal appearance. 'In some cells a partly normal and partly pathological character of the cell body is visible'. Neuroglia and white matter were normal. There are two drawings (×70 and ×500) by Ira Thompson van Gieson (1866–1913) whose name survives today in the connective tissue stain, and whose initials IvG may be seen on each plate. In the same year 1887 Wadsworth[7] of Boston described a further case, acknowledging the priority of Sachs's paper. Sachs's colleague, the ophthalmologist Knapp, contributed to the ensuing discussion.

## Later developments

Three years after his first communication Tay reported that three children in the original family had by then been affected.[3] Four years later he noted consanguinity of the parents in another case.[9] In 1888 Kingdon[6] mentioned Jewish parentage, but Sachs[10] accumulated further information: as a Jewish physician working among the large Jewish population in New York, by 1896 he had encountered 19 cases. The disease was 'almost exclusively observed in Hebrews', and he commented on how often parents were related by blood.

There the matter rested for nearly half a century until the galactolipid (GM$_2$ ganglioside) stored in the brain was identified.[11–15] Enzymologists discovered the enzyme which was missing in affected children,[16–17] and showed reduced concentrations in their parents.[18] The condition was thus defined as a lipid storage disease due in the infantile form (type 1) to deficiency of hexosaminidase A, with high concentrations of hexosaminidase B The way was then open to radical prevention Partial enzyme deficiency can be detected in carriers of the gene and affected fetuses during pregnancy.

## Tay and Sachs

The two discoverers looked at their observations rather differently. Warren Tay was interested in identifying the disease and its nature and left a particularly good record of the appearance of the optic fundi. Bernard Sachs in his first report was concerned not so much with the particular disease as with the relationship between mind and brain.[1]

> 'Our knowledge of the pathological substratum of the various forms of mental derangement is still very imperfect. In the majority of cases, there may be no marked changes in the structure of the brain; or, if there be any changes at all, they are entirely beyond our ken, and cannot be made out by our present methods of investigation As mental pathology is in its infancy it is but natural that we should first seek for structural changes in those conditions in which the departure from the normal is greatest, in which the mind is disturbed as a whole, and not merely with reference to a single part or faculty: though I shall at once declare my belief that derangement of a part of the mind means disorganisation, more or less complete of the entire mental mechanism.
>
> While we are even now in possession of many facts concerning the morbid structural changes in dementia paralytica changes that accompany the complete dissolution of a fully developed and once normal mind, we have busied ourselves but little with the morbid changes that often affect the brain, and consequently the mind also, when both are yet undergoing the process of evolution. These cases of retarded development, of idiocy, of mental imbecility, call them what you will, seem to me to possess a deep pathological and physiological interest. From the pathological changes found in these cases of extreme mental defects, we are entitled to draw an inference regarding the normal functions of those nervous elements here found deficient, and we may well argue with regard to such broad facts as an absolute lack of mentality, although it may be a long time to come before we shall be able to explain the morbid mechanism underlying fixed delusions, hallucinations, and the like, or to state exactly what the structural changes are in paranoia, in circular insanity, and in other grave mental troubles. The condition which I have the privilege of discussing before you to-day represents not only such changes as come about in the process of evolution, but represents changes of the earliest period of infantile development.'

I thank Dr Rosemary Stephens for advice and the librarians of the Royal Society of Medicine for assistance

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## Forty years ago

### Icterus neonatorum: its incidence and cause

*L Findlay, G Higgins, and M W Stanier (Oxford)—Arch Dis Child* 1947;**22**:65–74

In this paper Findlay and his colleagues set out to determine the incidence and cause of "physiological jaundice" With a definition of hyperbilirubinaemia as a plasma bilirubin >1 mg/dl (17·1 μmol/l), the incidence was 81% in 73 infants. No correlation was found between the concentration of bilirubin in umbilical cord blood and the maturity of the fetus, but premature infants were more likely to develop jaundice than mature ones Only four of the 73 infants, however, were below 35 weeks' gestation. A current theory that icterus neonatorum was due to excess haemolysis was dismissed on the basis of haematological studies, such as the haemoglobin curve during the first three months, and the absence of appreciable erythroblastosis or of reticulocytosis after the first few hours of life. On the other hand, the search for evidence of the failure of the neonatal liver to excrete bilirubin at the normal adult rate had to depend on tests that, by the standards of today, were inadequate for the purpose—for example, analysis of plasma proteins, the Takata-Ara reaction, and measurement of faecal bilirubin excretion Not surprisingly, most test results were inconclusive, but the authors, having excluded excess haemolysis on reasonably satisfactory evidence and having found some diminution in the excretion of bilirubin by the infant with jaundice compared with the infant without jaundice in the first few days of life, concluded that icterus neonatorum was due to hepatic immaturity.

**Comment.** It may be difficult for younger paediatricians to realise that in 1947 little or nothing was known of the conjugation of bilirubin in the liver cells, of the binding of bilirubin to albumin in the plasma and extracellular fluid, or of the enterohepatic circulation

(Leonard Findlay was one of the few British paediatricians with a truly international reputation before the second world war. In 1923 his appointment as Professor of Medical Paediatrics in the University of Glasgow was the start of the first University Department of Paediatrics in any British University He built a great reputation for his studies on rickets, rheumatic fever, and congenital syphilis He was among the first to integrate clinical paediatrics with the basic sciences Findlay was an autocrat with argumentative tendencies In 1930 in his early 50s he quarrelled with his colleagues in Glasgow and moved to the Princess Elizabeth of York Hospital in London In London, and later in Oxford, he never seemed to make the impact on international paediatrics that had characterised his work in Glasgow He died while the above paper was 'in press'.)

J H HUTCHISON

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## *Current topic*

# Unorthodox allergy procedures

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Paediatricians are increasingly having to pick up the pieces when ventures into bizarre allergy treatment meet with disaster This paper reviews some unorthodox allergy procedures in current use.

### Urine treatment

The patient's own urine is given orally, sublingually, intramuscularly, or topically.[1] The doses of urine for injection range from 2 ml for an infant to 8 ml for an adult. It is claimed that urine treatment can cure numerous diseases including eczema, asthma, and nocturnal enuresis The concept of 'auto immune urine treatment', which has also been used to treat 'intra-familial sensitivity' (allergy to members of one's family),[2] is based on the theory that a therapeutic dose of antigen is excreted in the urine.

### Applied kinesiology

It is alleged that if an antigen to which a subject is allergic—for example, an egg—is held near the patient's body, placed in the patient's palm, or administered as drops under the tongue, it will instantly cause a pronounced loss of muscle power which is easily detectable by an observer. When a patient is too young to cooperate, a surrogate is used.[3] The surrogate is tested alone and then retested when holding the child's hand, the results for the two subjects being subtracted to show the patient's allergies.

### Radionics

Radionics is based on the concept that man is submerged in an energy field which lies beyond the electromagnetic spectrum and is therefore undetectable by scientific instruments. The patient does not need to be present for radionic diagnosis or treatment, for the doctor and patient are said to be connected by a beam of energy, along which information can be transmitted that is relevant to the patient's health. The method uses extrasensory perception and a pendulum, accompanied by a 'witness' of the patient, usually a sample of hair.[4] Doctors with special gifts claim they can dispense with the pendulum and the witness, and test using merely the patient's name It is said that radionics can be used for the detection of all allergies, for the diagnosis of virtually all common diseases, and also for the identification of most individual bacterial pathogens.

### Pulse testing

It is reported that a tachycardia occurring five to 90 minutes after exposure to a food or inhaled material is a reliable pointer to food allergy.[5] Others have suggested that a slowing of the pulse rate is equally diagnostic

### Auricular cardiac reflex testing

It is claimed that if a substance to which a patient is allergic is brought within half an inch of the skin, then the auricular cardiac reflex (derived from a form of acupuncture) changes the wave form of the pulse at the wrist, enabling detection of the allergy Such testing currently uses dried food samples mounted in specially prepared filters, and it is said that using this technique 50 foods or chemicals can be tested in 15 minutes.[6]

### Vega testing

A Vegatest device is used to detect changes in the resistance to the flow of electricity over acupuncture points on the ends of fingers and toes. This is brought about by bringing particular substances in glass phials into series in an electrical circuit Vega testing is used to diagnose food allergy, chemical sensitivity, and 'organ stress'. It is reported that the observed changes in readings are partially psychokinetic effects and therefore dependent on the psyche of the practitioner.[7]

### Lymphocyte cytotoxicity

This test comprises the observation of morphological changes in white blood cells incubated simultaneously with a suspect antigen and a sample of the patient's serum.[8] The presence or absence and degree of damage caused to the leucocytes is claimed to be an indicator of the presence of food or chemical sensitivity, or both, and to given some indication of its severity.

### Enzyme potentiated transepidermal desensitisation

It is claimed that this technique exploits a potentiating effect of β glucuronidase when it is added to dilute allergen mixtures[9] A small plastic cup containing the appropriate desensitising fluid is placed over an area of skin which has previously been scarified using a blunt scalpel. The cup is left in place for 24 hours. A mixture of more than 70 allergens may be applied in the hope that important ones have been included. Identification of all the patient's allergies beforehand is not necessary. It is said that benefit may not occur until 12 months or more after treatment has been given

### Trace metal hair analysis

It is held that abnormal levels of trace metals may 'underpin' the development of food and chemical sensitivities.[6] Hair trace metal analysis is claimed to be a useful investigation in atopic disease, and any imbalance may be corrected by a mineral supplement.

### Intestinal candidiasis

In this supposed condition and the related entity 'dysbiosis', it is claimed that there is an imbalance of the flora of the gastrointestinal tract, which leads to a proliferation of *Candida albicans*. It is claimed that intestinal candidiasis can underlie food sensitivity and that such food sensitivity will not respond to a diet or desensitisation until the candidiasis itself has been diagnosed and treated.[10] Treatment is either with anti-*Candida* agents such as nystatin, or with sublingual drops.

### Intradermal skin testing

Unlike conventional intradermal allergy testing, with this method antigens are diluted to produce nine successively weaker concentrations and these are injected intradermally. A resulting weal is seen, and after 10 minutes assessed for lateral increase in size, blanching, hardness, and well demarcated edges. A 'positive' weal is said to have retained most of these features and to have grown at least 2 mm in diameter. It is reported that an injection of a concentrate may produce no reaction, whereas an injection of a dilute solution may result in a positive weal. It is further claimed that as the weal enlarges, symptoms related to the patient's complaint are provoked in 70% of subjects Finally, it is held that if increasing dilutions are injected at half hourly intervals, when a dilution is reached which causes no weal, symptoms disappear at once.[3 6] This dilution is then used in neutralisation therapy.

### Oral or subcutaneous neutralisation

Having determined the neutralising dose, neutralising solutions of all the relevant antigens are combined and then given either by sublingual drops or by subcutaneous injection.[3 6]

### Sublingual provocation

One or more drops of a dilute solution of an antigen or suspect substance are given sublingually, and the patient observed for adverse effects indicative of allergy to the test agent.[3]

### Conclusions

The feature common to all the above diagnostic and therapeutic methods is that their general application to atopic disease, food allergy, and other disorders has not been validated objectively.[11] This has never even been attempted with most techniques, and where it has the studies are either unsupportive or technically unsound.[11–13] There are other drawbacks to these methods: the inappropriate use of exclusion diets, often nutritionally inadequate, usually not supervised by a dietitian, and sometimes leading to severe malnutrition or persistent dietary obsession[12], false diagnosis of disease where none exists—for example, North Sea gas allergy[11 12]; and great expense.[11]

In the United Kingdom unorthodox approaches are largely used by doctors without any specialist training, who operate from private allergy clinics where careful appraisal and follow up may not be carried out. The onus to prove the validity, if any, of these techniques lies with the proponents of such forms of diagnosis or treatment. All these methods must be regarded at best as experimental and their use confined to properly designed investigational studies.

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## *Personal view*

# Case conferences for child abuse

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Case conferences have been an integral part of child abuse procedures since 1974 when the recommendations of the inquiry into the death of Maria Colwell were published. The case conference is a multidisciplinary forum for the sharing of information, for discussion, and for making recommendations to social services departments, which are ultimately responsible for the welfare of the child under discussion. In principle, therefore, case conferences are advisory rather than executive. In practice, considerable weight is usually attached to their recommendations. In some areas children leave hospital on the day of the case conference as a result of its decisions. In effect, the director of social services has delegated responsibility in advance to the local office managing the case. In other areas the director insists on vetting personally all case conference recommendations. Even so it is relatively rare for such recommendations to be over-ruled.

Few people love case conferences, and many hate them. Certainly their procedures are open to criticism on many fronts.

### WASTAGE OF TIME AND RESOURCES

Case conferences can take two to three hours and involve 20 or more people. They can therefore cost between £500 and £1000 per conference in terms of working hours lost.

### RAMBLING UNFOCUSED DISCUSSION

This contributes to the waste of time and resources, and if it is allowed to occur is largely the fault of the chairman. If members do their homework and the conference has all the necessary information to hand most decisions are so easy as to be foregone conclusions. One paediatrician known to the author used to forecast each case conference decision in writing and place it in a sealed envelope on the table before the conference. Having been proved right, he would then open the envelope at the end of the conference and reveal to members how much time they had wasted.

### DOMINANCE OF HIERARCHIES

Too often the more junior social workers or health visitors dealing directly with the family refrain from expressing their opinions because they are inhibited in front of their seniors. A good chairman should detect this and encourage them to speak up.

### BUREAUCRATIC DECISION MAKING

Child care is a dynamic discipline requiring judgment and skill. Case conferences share the defects common to all committees in that they tend to discourage these attributes in searching for a consensus. This can lead to a 'safety first' mentality when most of the children are taken into care, rather than trusting the judgment of one key professional who feels that rehabilitation is the preferred option. Alternatively, the security derived from being part of a collective decision making process can lead to professionals colluding with each other to return children to situations of high risk, secure in the knowledge that there is safety in numbers and that the social services will have to shoulder most of the blame anyway.

This area of criticism seems to constitute quite a weighty attack on the whole structure of case conferences. On closer inspection, however, these criticisms are directed at human frailty itself. Again, the leadership of a chairman who forces the members to answer crucial questions will go a long way to prevent this failure.

### IMPORTANT ABSENTEES

Busy consultant paediatricians occasionally resort to sending their juniors to case conferences in their place. This is to be deprecated as it is difficult for a senior house officer or registrar to speak with sufficient authority, either at the case conference or subsequently in court. Another common important absentee is the legal adviser to the social services. Again this is regrettable as it blocks decision making and wastes the time of those present.

The least defensible reason for important absentees is the deliberate failure to invite key professionals. The invitation list for the case conference that decided to 'rehabilitate' Jasmine Beckford is a noteworthy example.[1]

SITTING ON THE FENCE BY PROFESSIONALS

The diagnosis of non-accidental injury is clearly the responsibility of the paediatrician, who, if he sits on the fence, does a disservice to the child the parents, and the members of the case conference. Similarly, responsibility for the diagnosis of growth failure and developmental retardation due to neglect clearly lies with the paediatrician, who is also best placed to inform other conference members (and eventually the magistrates) of the seriousness of this condition. In older children who are subject to emotional abuse or deprivation an increasing responsibility rests with child psychiatrists who are themselves capable of sitting on the fence.

One possible reason for sitting on the fence by doctors is that they find it natural to remain noncommittal unless they can make a diagnosis 'beyond all reasonable doubt'. They should be reminded that this degree of proof is required only in obtaining a criminal conviction and that the standard of proof required in the magistrates' court to obtain a care order is 'on the balance of probabilities'.

PHILOSOPHICAL DIFFERENCES BETWEEN PROFESSIONALS

An undercurrent of ideological disagreement is at the root of many 'stalled' case conferences where discussion goes round in circles. The commonest controversy is between those who favour 'rehabilitation wherever remotely possible' and those who favour the 'care option' in one form or another. This same controversy often simmers beneath the surface at many academic meetings on child abuse.

Because opponents seldom bring their ideological differences out into the open, it appears that their disagreement is simply about the particular case under discussion. The same professionals can have the same argument at 20 consecutive case conferences. Ideally, the chairman should recognise what is happening and invite the conference to acknowledge the gulf of reasoning that lies between some of the participants. Perhaps he can gently suggest that the opponents settle their differences in private.

PRESENCE OF PARENTS AS FULL MEMBERS OF CONFERENCE

Apparently, this practice is quite common in some areas. It is difficult to think of a better recipe for a collusive relationship with abusive parents against the interests of the child. A recent circular from the DHSS strongly condemns parental participation in this manner.[2]

LAST MINUTE DOWNGRADING OF A CASE CONFERENCE TO A CASE DISCUSSION

This is an infuriating device occasionally used by social services as a form of passive resistance. In essence it is a very simple manoeuvre, whi involves failing to invite key professionals, turni up without a chairman or legal adviser, and n taking any minutes. From bitter experience I ha found that the only effective counter is to refuse participate and to renew requests for a full ca conference

UNDUE RELIANCE ON LEGAL ADVICE

Some legal advisers like to maintain a 100% batti average in the courts and accordingly err on the si of caution regarding care proceedings. Such pes mistic advice should not be accepted uncritica when members feel strongly that statutory control needed Legal advisers are the servants of soc services not the masters, and can be instruct accordingly.

None of these extensive criticisms is aim directly at the institution of the case conferen itself; they are aimed at areas of practice not principle, and all the areas criticised are amenable correction.

## The ideal case conference

The conference should have a time limit of one ho and should start promptly. The chairman should from social services but with no direct role in t management of the case. He should attempt combine the bluntness of Churchill with the wisdo of Solomon. The social worker (and whe appropriate the health visitor and paediatricia should have prepared duplicated reports which a handed round and studied for five to 10 minutes. N one should be allowed to read out their reports. T contents of the reports are then open to discussio and other contributions should be invited T chairman then asks the conference to address its to the following questions:

(i) have significant episodes of abuse or negle occurred?
(ii) why have they occurred?
(iii) how likely are they to recur?
(iv) what action is required?

If the answers to these questions are clear c discussion should be brief and to the point. If stro disagreement exists the chairman should allow t opposing views to be put clearly (by specia appointed devil's advocates?) and then invite t conference as a whole to commit itself to one other view rather than strive for too long to reach unsatisfactory compromise. Whether decisio should actually be put to the vote (and wheth everyone who attends is equally entitled to vote) i matter for debate. Certainly clear opportun should be given for individual members to reco their opposition to decisions, and as a last resort to dissociate themselves from the management of the case.

Despite the many criticisms of practice outlined above, most paediatricians would not dream of questioning the place of the case conference in child care work. Surprisingly, the Society of Clinical Psychiatrists holds a different view. In a paper, from which extracts were published in this journal recently,[3] the authors argue that case conferences are 'pernicious . . . dangerously irresponsible . . . inherently ineffective,' and 'should be abolished'. The authors protest at the gross breaches of confidence that case conferences lead to for 'their clients'—that is, the parents.

Paediatricians have children as their clients and will surely find this stance astonishingly negative. A detailed rebuttal of this view has already been made in this journal.[4] For better or worse, case conferences remain a vital part of the procedure for dealing with child abuse, and it is difficult to imagine any satisfactory alternative.

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## *Short reports*

# Dicarboxylicaciduria and secondary carnitine deficiency in glycogenosis type IV

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SUMMARY A 3 year old boy developed an unusually mild form of glycogen storage disease type IV. Metabolic investigations showed severe abnormalities of fatty acid and carnitine metabolism. A muscle carnitine deficiency was found. Treatment with L-carnitine orally led to a notable improvement in muscle strength.

The patient was first seen at the age of 16 months with hepatosplenomegaly and hypotonia. The liver was 4 cm and the spleen 2 cm below the costal margin. Mental development was normal but motor development was severely retarded. Tendon reflexes were weak. Hypotonia was generalised but most pronounced in the legs. The child could not sit unsupported and could not stand up or walk. Computed tomography of the brain, electromyography, electrocardiography, and echocardiography all yielded normal results. Laboratory tests showed mild liver dysfunction (serum glutamic oxaloacetic transaminase activity 186 U/l and serum glutamic pyruvic transaminase activity 67 U/l). Low free and total plasma carnitine concentrations were found (table). Results of other laboratory tests were normal. No evidence of a metabolic disorder was found. Liver and muscle biopsy specimens were taken. In the liver micronodular and macronodular cirrhosis was found; periodic acid Schiff positive material which was fairly resistant to diastase was present in the hepatocytes. Electron microscopic studies showed abnormal glycogen deposits in the cytoplasm. In the muscle only mild non-specific changes were seen, but no abnormal accumulation of glycogen was found.

The combination of the clinical findings of hepatosplenomegaly and disturbed muscle function and the histological finding of glycogen storage in the liver led to a diagnosis of glycogen storage disease type IV, which was confirmed by the finding of a branching enzyme deficiency in white cells (0·5 nmol glucose-1-phosphate/min/mg; control value (n=3) 237–355) and in cultured fibroblasts (58 nmol glucose-1-phosphate/min/mg; control value (n=9) 490–1300).

At the age of 22 months high concentrations of ketone bodies and dicarboxylic acids were found in a

Table *Effect of different metabolic conditions on measurements of fatty acid metabolism*

| | *Plasma* | | | | *Urine* | | | |
|---|---|---|---|---|---|---|---|---|
| | *Glucose (mmol/l)* | *Carnitine (mmol/l)* | | *β Hydroxybutyric acid (mmol/l)* | *Carnitine (μmol/mmol creatinine)* | | *β Hydroxybutyric acid (mmol/l)* | *Dicarboxylic aciduria* |
| | | *Total* | *Free* | | *Total* | *Free* | | |
| Aged 16 months, fasted for 10 h | 4·5 | 21 | 8 | Not done | 56 | 7 | Not done | Absent |
| Aged 22 months | | | | | | | | |
| Fasted for 10 h* | | | | | 262 | 4 | 7·8 | ++++ |
| Not fasted | 3·6 | 39 | 27 | 0·48 | 19 | 2 | 0·01 | Not done |
| Fasted for 16 h | 2·4 | 22 | 4 | 1·73 | 84 | 6 | 2·07 | +++ |
| After treatment with L-carnitine for two months, fasted for 10 h | 3·8 | 54 | 44 | 0·01 | 951 | 114 | 0·58 | + |

*Urine sample only

morning urine sample (table). The patient was given a standard fasting test, which had to be stopped after 16 hours because of symptomatic hypoglycaemia Low plasma concentrations of free carnitine were noted, in addition to dicarboxylicaciduria and ketonuria (table). Carnitine concentrations were measured in liver and muscle biopsy specimens. In the liver specimen total carnitine concentrations were normal at 6·8 nmol/mg non-collagenous protein (control value (n=3) 3·9–4·7). All the carnitine, however, was present in the form of the ester In the muscle biopsy specimen severe carnitine deficiency was found: total carnitine concentration was 3·7 nmol/mg non-collagenous protein (control value (n=4) 13·0–19·3).

At the age of 26 months a diet rich in protein and low in fat was prescribed, with frequent meals being taken to prevent mobilisation of fatty acids. The diet was supplemented with L-carnitine 100 mg/kg/day. Within a month the boy had become more active and started to explore; muscle strength improved considerably. At the age of 33 months he could pull himself on to his feet and walk a few steps without support, but muscle strength was still mildly reduced. Fasting ketonuria and dicarboxylicaciduria had almost disappeared (table).

## Discussion

Glycogen storage disease type IV is a rare recessively inherited disorder of glycogen metabolism caused by a deficiency of the branching enzyme; only about 20 other cases have been reported [1] Clinical features include failure to thrive, hepatosplenomegaly, and early cirrhosis of the liver. Most patients die in their second year of life. The course of the disease in this patient was unusually mild as he was still well at the age of 3. McMaster *et al* suggested that neuromuscular abnormalities in these patients correlate fairly well with abnormal deposits of polysaccharides in skeletal muscle and in the central or peripheral nervous system or both [2] In our patient, however, no abnormal storage of glycogen was found in the muscle tissue.

Ketosis with dicarboxylicaciduria and a tendency to fasting hypoglycaemia has been described in other types of glycogen storage disease but has not been reported before in patients with type IV disease [3] The profile of the urinary dicarboxylic acids was typical of ketotic dicarboxylicaciduria.[4] It reflects the excessive flux of fatty acids through the β oxidation pathway in these patients, who are not able to use glycogen stores as a buffer for glucose homoeostasis during fasting. The high ratios of ester carnitine to free carnitine in plasma and liver are also compatible with these findings Two factors may have contributed to the carnitine deficiency in muscle[5]: the increased urinary excretion of carnitine as acylcarnitine esters, resulting from the excessive intramitochondrial beta oxidation of fatty acids (table), and the reduced endogenous synthesis of carnitine by the liver due to liver cirrhosis. The improvement in muscle strength after starting the treatment with carnitine was rewarding. Our findings suggest that muscle carnitine deficiency is an important cause of muscle weakness in patients with glycogen storage disease type IV.

We thank Dr O P van Diggelen, Erasmus University, Rotterdam, for the assays of the branching enzymes

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# Mean arterial blood pressure and neonatal cerebral lesions

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SUMMARY Computerised continuous measurement of mean arterial blood pressure (MAP) and serial cranial ultrasonography in 33 infants of <31 weeks' gestation showed that a MAP of <30 mm Hg for over an hour was significantly associated with severe haemorrhage, ischaemic cerebral lesions, or death within 48 hours. No severe lesions developed with a MAP ≥30 mm Hg.

Disturbances of blood pressure may be important in the pathogenesis of intracranial lesions in preterm infants. Periventricular haemorrhage and leucomalacia have been attributed to excessive and insufficient cerebral blood flow, respectively,[1-3] and there is an association between hypotension and periventricular haemorrhage.[4 5] Limitations of previous studies have included incomplete delineation of cerebral lesions, intermittent blood pressure measurements (missing short term variations), and failure to exclude infants with cerebral lesions at the start of recording. We overcame these problems by using computerised, continuous acquisition of data and serial high resolution cranial ultrasonography, and by excluding any infant with a lesion at the start of recording.

## Patients and methods

Infants of 26–30 weeks' gestation were eligible for the study, carried out from February 1985 to September 1986, provided they had an umbilical artery catheter in place by the time they were 6 hours old, a normal initial cranial ultrasound scan, and no evidence of congenital abnormality. Umbilical artery catheters incorporating an oxygen electrode and a side hole (Neocath, Biomedical Sensors Ltd, High Wycombe, UK) were advanced to the level of T8–T10 and infused through flushing devices (Intraflo, Sorensen Research, Utah, USA). Signals were relayed from a transducer (Medex MX800, Medex Inc, Haslingden, Rossendale, UK) to a neonatal monitor (Model 431A, Tektronix Ltd, Harpenden, Herts, UK) interfaced with an analog digital converter and an Apple IIe microcomputer. We chose this method in preference to intermittent recording, which misses short term fluctuations (figure). Arterial waveforms were collected over 20 second periods and the true mean arterial pressure (MAP) derived. Data were stored on floppy disk and the 20 second cycles repeated. Ultrasound scans were made at least daily during the first week and then weekly until discharge, with an ATL Mark III sector scanner with multifrequency head (3/5/7·5 MHz).

Thirty three infants were entered into the study; 28 were having mechanical ventilation, and five required headbox oxygen for the respiratory distress syndrome. Treatment was independent of the results of the study, the clinicians having no access to the data collected. Pethidine and pancuronium were given when required, and plasma or 5% human albumin was given slowly (10–15 ml/kg) if perfusion was considered inadequate. Seven infants received inotropic support for extreme underperfusion (dopamine or dobutamine, or both, in a dose of 5–10 µg/kg/min) starting on average 10½ hours after birth.

Statistical analysis of differences in proportions was done using the $\chi^2$ square test with Yates's correction.

## Results

Data recording started an average of three hours

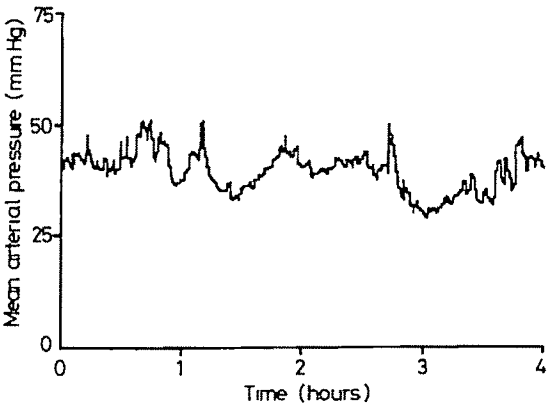

Figure *Mean arterial pressure from an infant of birth weight 1000 g showing spontaneous short term fluctuations* after birth (range 2–5 hours) and continued for an average of 86 hours (range 30–348) Cranial ultrasound appeareances were classified by LSdeV, who did not know the MAP results, and the MAP results were analysed by VMA, who did not know the ultrasound classification

Ultrasound appearances were classified as normal; showing mild changes (for example, germinal layer, small intraventricular haemorrhage, or transient periventricular densities of three to 12 days' duration); or showing persistent severe lesions (for example, extensive haemorrhage or periventricular leucomalacia).[6] The latter group also included infants who died at less than 48 hours old as there may have been insufficient time for ischaemic changes to become visible.

MAP values were classified as follows: always ≥35 mm Hg; 30–34 mm Hg for longer than one hour but never <30 mm Hg; 25–29 mm Hg for longer than one hour but never <25 mm Hg; and <25 mm Hg for longer than one hour. Values of ≤29 mm Hg were found only in the first 24 hours, before cerebral lesions developed, and never occurred for the first time after 24 hours. In the two infants who died hypotension was not a terminal event, having been present for 22 hours. Increase in blood pressure variability was not seen when circulatory support was given.

The outcome was significantly worse the lower the MAP (table). None of the infants who maintained a MAP of ≥30 mm Hg developed severe lesions. Infants with a MAP of <30 mm Hg had significantly more severe lesions and early deaths than those with a MAP of ≥30 mm Hg ($p<0{\cdot}01$). The average weight of infants with an MAP of ≥30 mm Hg was 1040 g (range 700–1700) and with an MAP of <30 mm Hg it was 1060 g (range 700–1600). The average gestational age of those with an MAP of ≥30 mm Hg was 27·8 weeks (range 26–30) and of those with an MAP of <30 mm Hg 27·7 weeks (range 26–30). Thus the differences in MAP between the two groups were not due to differences in weight or maturity.

Table *Grouping of infants by lowest mean arterial pressure and cranial ultrasound appearances*

| *Mean arterial pressure >1 hour (mm Hg)* | *Cranial ultrasound appearances* | | |
|---|---|---|---|
| | *Normal* | *Transient* | *Severe* |
| ≥35 | 5 | 1 | 0 |
| 30–34 | 0 | 6 | 0 |
| 25–29 | 0 | 6 | 3 IVH/bilateral extension, IVH/infarct/hydrocephalus, IVH/PVL |
| <25 | 1 | 5 | 6 IVH/early death, IVH/early death, IVH/extension, IVH/extension; IVH/extension/infarct, PVL |

IVH=intraventricular haemorrhage, PVL=periventricular haemorrhage

## Discussion

Other studies have placed most emphasis on the instability of blood pressure or its transition from low to fairly high pressures[3–5]; in contrast, we have shown a significant association between sustained low mean arterial pressure and cerebral lesions or early death.

MAP was chosen in preference to systolic pressure alone because it is less subject to error from damping and is used to calculate cerebral perfusion pressure. Systolic pressure does not represent the whole of the cardiac cycle, whereas MAP does. Hypotension may relate to the underlying diseases or treatments, but whatever the cause intervention to maintain MAP needs further evaluation in terms of morbidity and mortality.

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# Carbon monoxide production in ventilated premature infants weighing less than 1500 g

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SUMMARY Mean pulmonary excretion rate of carbon monoxide in 13 premature babies on ventilators was significantly higher ($p<0\cdot001$) than that of 19 healthy infants born at full term. This correlated with carboxyhaemoglobin concentrations in blood, indicating that the premature infants on ventilators produced abnormally large amounts of bilirubin

Exaggerated hyperbilirubinaemia, requiring phototherapy or exchange transfusion, continues to be a common problem complicating the management of very low birth weight premature infants being nursed on ventilators. We have previously reported that healthy premature infants have higher bilirubin production than those born at term[1] and have shown that there is an association between the pulmonary excretion rate of carbon monoxide (VeCO) and the blood carboxyhemoglobin saturation corrected for inspired carbon monoxide content ($HbCO_c$).[2] Both the VeCO and the $HbCO_c$ are thought to be suitable indices of bilirubin production.[3-5] For technical reasons it has not previously been possible to measure the VeCO of ill very low birthweight premature infants, in particular, those receiving mechanical ventilation. In the present study, the VeCO was calculated in a group of very low birthweight premature infants who were nursed on ventilators during the first few days of life. The association between the VeCO and the $HbCO_c$ was also studied.

## Patients and methods

Infants who weighed less than 1500 g at birth and who were being nursed on ventilators were eligible for the study Written informed consent was obtained from the parents of each baby.

Ventilatory support varied from infant to infant. All the infants had umbilical artery catheters or peripheral intravenous lines in place so that parenteral fluids could be given. None had haemolytic disease with a positive Coombs' test. The mean (SD) birth weight of the infants was 950 (290) g, and the mean (SD) gestational age was 28 (3) weeks. The mean (SD) age at which the initial VeCO calculations were performed was 2 (2) days

All the infants received ventilatory support from either a Bourns BP200 or a Sechrist Model IV-100B infant ventilator Both of the units were set up in a time cycled, pressure limited configuration with a constant gas flow of 5–10 litres/minute in the ventilator circuit. Before the gas samples for calculation of the VeCO were collected the babies breathed a gas mixture that was passed through a Hopcalite converter constucted to fit into the ventilator circuits. This substantially reduced the concentrations of carbon monoxide in the gas entering the ventilators (<20 parts per billion), thus improving the sensitivity of the measurement of the carbon monoxide content of the collected samples.

The carbon monoxide content of the gas samples was measured using a gas chromatograph fitted with a column packed with molecular sieve 5A (Altech Associates, Inc , Los Altos, California, USA) and a reduction gas detector (Trace Analytical, Menlo Park, California, USA). VeCO was calculated using the equation:

$$\text{VeCO}(\mu l/kg/h) = \frac{[CO_{out}-CO_{in}](\mu l/l)\times \text{flow}(1/\text{min})\times 60(\text{min}/h)}{\text{Body Wt(kg)}}$$

where flow=the flow through the ventilator circuit, $CO_{out}$=the CO content of the gas in the ventilatory circuit distal to the patient, and $CO_{in}$=the CO content of the gas in the ventilatory circuit proximal to the patient. The $CO_{out}$ and $CO_{in}$ gas samples were drawn from the ventilator circuit through a sampling port over two to three minutes so that transient fluctuations in the content of carbon monoxide in the gas flowing through the circuit could be time averaged. Gas leaks in the ventilator circuit were negligible (less than 1%) Based on previous measurements of flow volume loops in infants on ventilators, we excluded those subjects with gas leaks around the endotracheal tube which were thought to comprise more than 5% of that infant's ventilation during the sampling period.

Blood samples (100 μl) for calculating HbCO concentrations were taken 60–75 minutes after the babies began breathing the CO depleted gas mixture, at the same time as the sampling for the measurement of VeCO. The details of the method

Table *Comparison of mean (SD) estimates of bilirubin production by healthy infants born at term, healthy premature infants, and premature infants on ventilators*

| | *Healthy infants born at term* | | *Healthy premature infants* | | *Premature infants on ventilators (n=13)* |
|---|---|---|---|---|---|
| | *Normal (n=19)* | *Jaundiced (n=5)* | *Non-jaundiced (n=15)* | *Jaundiced (n=8)* | |
| Hb (g/dl) | 19 0 (2 7) | 17 5 (3 0) | Not done | Not done | 14 2 (2 0)‡ |
| VeCO (μl/kg/hour) | 13 4 (3 2)* | 18 5 (4 5) | 15 1 (4 1)† | 19 5 (5 5) | 22 8 (5 5)*† |
| $HbCO_c$ | 0 45 ( 13) | 0 52 ( 10) | Not done | Not done | 1 06 ( 40)‡ |

*$p<0.001$, †$p<0.001$, ‡$HbCO_c$ and Hb available on 12 of 13 infants

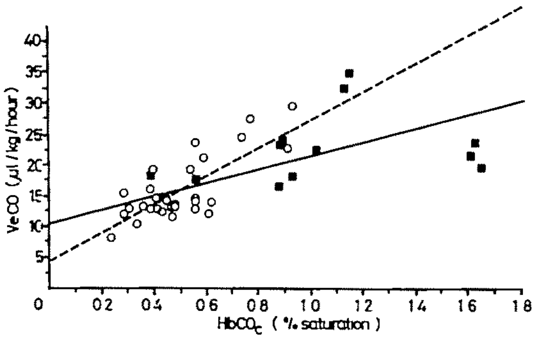

Figure *VeCO v $HbCO_c$ for preterm (■) and term (○) infants. The regression line for the term infants alone (– – –) is VeCO=23 4 $HbCO_c$+4·2, and the line for both the preterm and term infants combined (———) is VeCO=11·0 $HbCO_c$+10 6*

for HbCO analysis have been described previously.[6]

The significance of differences was measured using Student's *t* test and linear regression analysis.

## Results

In calculating the average VeCO, $HbCO_c$, and haemoglobin concentrations for the group, we used only one set of data for each infant The table summarises the previously reported data on premature infants and those born at full term, and the present data on the very low birthweight premature infants on ventilators.

The figure shows the association between the VeCO and the $HbCO_c$. Data for the 30 infants born at full term and the 12 ventilated very low birthweight premature infants for whom both the VeCO and the $HbCO_c$ were available are presented. The regression line describing these data is VeCO=11·0 $HbCO_c$+10·6 ($r=0.65$). Also presented is the regression line for the 30 infants born at full term alone. The regression line for these data is: VeCO=23·4 HbCOc+4·2 ($r=0.77$).

Ten of the very low birthweight ventilated preterm infants had blood gas analysis performed (one capillary, nine arterial) at the time of their VeCO determination. The $PCO_2$ ranged from 4·0–6·5 kPa (mean (SD) 5·5 (0·76 kPa), and the $PO_2$ ranged from 6·3–8·8 kPa, mean (SD) 7·4 (0·7) kPa).

## Discussion

We believe that this report presents the first data on the carbon monoxide excretion rate, as an index of bilirubin production, in very low birthweight premature infants on ventilators. These infants had a mean VeCO which was significantly higher than that of healthy infants born at full term ($p<0.001$). The aetiology of this increased rate of carbon monoxide production, which indicates increased production of bilirubin, is not fully understood. Although this study was not designed to identify the specific clinical factors that might contribute to an increase in bilirubin production, it is known that exposure of the fetus to drugs taken by the mother that can affect red cell life span (for example, anaesthetic agents such as bupivacaine), multiple neonatal transfusions of red cells with reduced life span, and an inherent decrease in the life span of fetal red cells are commonly associated with very low birthweight prematurity. The correlation between VeCO and $HbCO_c$ reflects greater variability in the association of these indices between the very low birthweight infants on ventilators when compared with infants born at full term.

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# Successful suprapubic aspiration of urine

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SUMMARY When the bladder of neonates requiring suprapubic aspiration of urine was shown to contain urine on ultrasound scanning, suprapubic aspiration was successful on the first attempt in all cases. Without prior scanning only 36% of first attempts at aspiration were successful.

Accurate diagnosis of urinary tract infection in neonates is important[1]; collection of urine is preferably by suprapubic aspiration, as bag collections are often contaminated.[2] Unfortunately, suprapubic bladder aspiration, even by experienced medical staff, often requires repeated attempts This is painful for the infant and may lead to complications such as infection and bowel perforation. This study was performed to assess ultrasound scanning of the bladder as an aid to successful aspiration of urine.

## Patients and methods

The infants studied were from the neonatal intensive and special care units at the Royal Children's Hospital Melbourne Forty three consecutive infants requiring suprapubic aspiration of urine as part of their infection screen were studied. Suprapubic aspiration of urine was performed as described by Nelson and Peters.[3]

For 15 of those infants, an ultrasound ATL 300 machine was available and their bladders were scanned for the presence of urine. Aspiration was only attempted if urine was seen on ultrasound scan. If urine was not seen the infant was rescanned at 10–15 minute intervals until it was seen, and only then was aspiration attempted. The other 28 infants required suprapubic aspiration when the ultrasound machine was not available. A record of the number of attempts needed to obtain a sample was made. If after three attempts no urine was obtained, a bag collection was performed.

A further 40 infants not requiring suprapubic aspiration were scanned for the presence of urine in their bladder. If no urine was detected they were rescanned at 10–15 minute intervals until urine was detected.

## Results

Of the 15 neonates scanned by ultrasound prior to aspiration, urine was shown to be present in the bladder within 30 minutes in all cases. Aspiration attempted when urine was seen was successful on all 15 occasions. Of the 28 neonates not scanned, only 10 (35%) had successful aspiration of urine on the first attempt. No urine was obtained despite three attempts at suprapubic aspiration in seven of these infants and bag collection was done instead. Of the 40 neonates scanned at random, 13 (33%) had urine detected within the bladder. Urine was detected in the bladders of all but one of the 27 remaining neonates within 45 minutes.

## Discussion

If the bladder was seen to contain urine on ultrasound scan suprapubic aspiration was successful on the first attempt in all cases. In all but one case urine could be detected within 45 minutes by ultrasound scanning. The infant not showing bladder filling after this period was found to have renal agenesis.

Without scanning, only 36% of first attempts at suprapubic aspiration were successful. This correlated well with the random bladder scans performed on other infants, where only 33% had urine detected in their bladder at the time of initial scanning. The technique of bladder scanning for urine content can be taught to resident medical staff in less than 10 minutes.

With the increasing availability of ultrasound machines on neonatal wards, paediatric wards, and even in the community, bladder aspiration will present less of a problem to medical staff and result in less pain to babies.

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# Early congenital syphilis and severe haematological disturbance

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SUMMARY The early clinical signs and symptoms of congenital syphilis are diverse but, if undiagnosed, signs of the disease may subside until the late stigmata appear. We report a case that illustrates that the haematological signs and symptoms may be so severe as to mimic a diagnosis of leukaemia or disseminated malignant disease.

Early congenital syphilis is rarely diagnosed in the United Kingdom; an average of 12 cases a year were reported between 1973 and 1982.[1] Clinical signs are usually absent at birth and during the first few weeks of life. The earliest findings may be non-specific and subsequent symptoms and signs are diverse, if untreated they may subside until the stigmata of late congenital syphilis appear. The chief pitfall in the diagnosis of early infection is paediatricians' failure to include it among the differential diagnoses of a large number of illnesses in infancy. We report a child with early congenital syphilis who presented with such profound haematological disturbance that leukaemia or disseminated malignant disease were considered to be the most likely diagnoses.

## Case report

An 8 week old baby girl presented with a one week history of rash, irritability, and increasing pallor. She had been born at 36 weeks' gestation, weighing 2400 g, after a pregnancy complicated only by uncertain dates. Serological screening at about 22 weeks' gestation showed a negative reaction for syphilis using the Venereal Diseases Research Laboratory (VDRL) and *Treponema pallidum* haemagglutination (TPHA) tests. She had mild jaundice which was treated with phototherapy for 24 hours and subsequently resolved. On examination she was feverish with extreme pallor and a widespread rash characterised by circular, erythematous (almost papular) lesions, and some superficial scaling. There were a few bruises over the trunk and the liver edge was palpable 8 cm, and the spleen tip 6 cm, below the costal margins. Examination of the fundi, mucosal surfaces, perianal region, and genitalia yielded normal results.

Initial haematological investigations showed a haemoglobin concentration of 2·9 g/dl, a platelet count of $<10\times10^9/l$, a white cell count of $22·4\times10^9/l$ (neutrophils 11%, lymphocytes 61%, monocytes 4%, metamyelocytes 3%, myelocytes 1%, blast cells 20%), and the ratio of nucleated red cells to white cells was 2:100. Examination of the peripheral blood smear confirmed the presence of immature 'blast-like' cells. Coagulation screen yielded normal and direct antiglobulin test negative results. Despite the severity of the thrombocytopenia and poor initial response to transfusion of platelets there was no obvious evidence of bleeding. Liver function tests were abnormal with aspartate aminotransferase activity of 66 IU/l (normal <50); alanine aminotransferase activity of 60 IU/l (normal <40); alkaline phosphatase activity of 1147 IU/l (normal for age); bilirubin concentration of 44 μmol/l (normal <17); direct bilirubin concentration of <5 (normal); total protein concentration of 49 g/l (normal 55–75); and albumin concentration of 15 g/l (normal 30–50).

Chest x-ray picture was normal, but a skeletal survey showed periosteal reaction along the shafts of the long bones with some metaphyseal irregularity.

Bone marrow aspirates were obtained from the anterior tibia and both posterior iliac crests. The samples were consistently hypocellular but showed a population of immature cells (25%), with morphological features suggesting monocytoid differentiation. There were, in addition, appreciable numbers of large histiocytic cells (17%), indicating erythrophagocytosis. Cytochemical stains using periodic acid Schiff, Sudan black, and alphanapthyl esterase were negative. A few blast cells were faintly positive to acid phosphatase. Surface marker studies with a panel of monoclonal antibodies showed a broad response (My9 40%, Mo1 49%, SmIg 30%, $I_2$ 30%, My 7 25%, J5 <5%, and Tdt negative).

Disseminated malignant disease seemed to be the most likely diagnosis, with malignant histiocytic disease, acute monocytic leukaemia, or histiocytosis X as the most favoured alternatives. The possibility of congenital infection was considered but thought less likely in view of the severity of the haematological abnormalities. Initial management included transfusions of blood and platelets and, pending results of bacterial cultures and viral serology, treatment with broad spectrum antibiotics (azlocillin, gentamicin, and flucloxacillin). In view of the difficulty in interpreting the haematological results a skin biopsy was performed. It was notable, however, that the skin rash had improved after antibiotic treatment, as had the infant's general condition, with resolution of the fever and regression of the hepatosplenomegaly (figure). On histological examination the skin biopsy specimen showed a histiocytic/lymphocytic infiltration, although the appearances were not diagnostic.

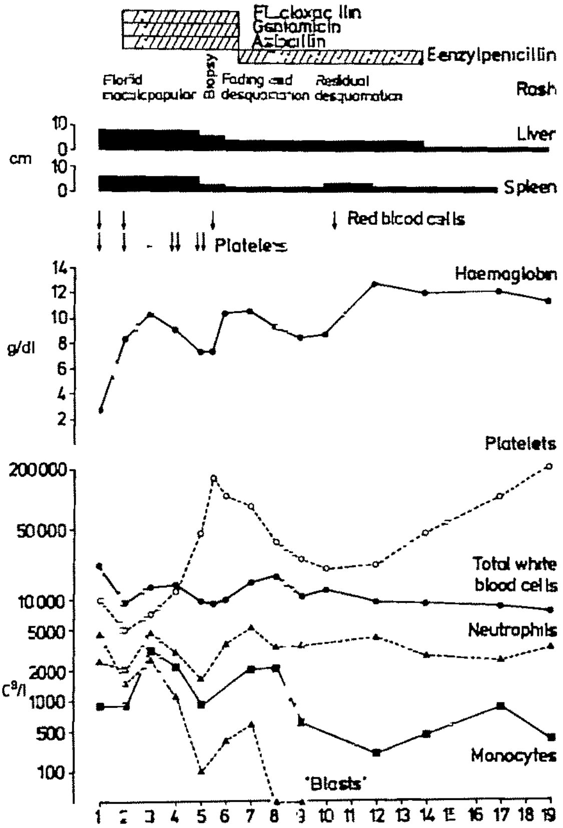

Figure *Clinical, haematological, and therapeutic data from time of admission.*

Six days after admission, VDRL and TPHA tests were reported as being positive in samples taken on admission from both mother and baby, suggesting a diagnosis of congenital syphilis. Subsequent results from the reference laboratory confirmed this as follows: baby—VDRL 1:64, TPHA 1:512, and cerebrospinal fluid negative to both; mother—VDRL 1:64, and TPHA 1:1024. Antibiotic treatment was changed to benzyl penicillin, the total dose exceeding the WHO guidelines for adequate treatment.[2] The baby made an uneventful recovery. The rash desquamated and faded, hepatosplenomegaly regressed completely, and the blood count returned to normal after 10 days. The family was referred to their local genitourinary clinic for follow up and the baby remained well and was developing normally one year after diagnosis.

## Discussion

The characteristic clinical changes of early congenital syphilis are widespread and include rash, severe rhinitis, moist lesions at mucocutaneous junctions, painful limbs (often presenting as pseudoparalysis), lymphadenopathy, and hepatosplenomegaly. Jaundice is common, as is hypoproteinaemia which may cause oedema. Of the haematological findings, anaemia commonly occurs; almost 90% of children with early congenital syphilis diagnosed postnatally were described as anaemic in a recent large review.[3] The incidence of thrombocytopenia is not clear, although the association of increased platelet turnover (with or without thrombocytopenia) with congenital viral infections, syphilis, and toxoplasmosis is well known.[4] The severity of the marrow reaction in this child was striking, with prominent immature monocytoid and mature histiocytic cell populations together with a leucoerythroblastic response in the peripheral blood, mimicking disseminated malignant disease. A similar but less severe presentation was described in one of nine infants with haematological signs and symptoms of congenital syphilis.[5]

The negative results of the antenatal serological tests imply that the mother was either incubating the infection at that time, or had acquired it later in pregnancy. A similar sequence of events was seen in five of seven women whose infants were later diagnosed as having early congenital syphilis in a survey from the Mersey region,[1] which raises the question of whether serological screening should be repeated during the third trimester.

The case we report emphasises the serious implications of early congenital syphilis, and shows that the haematological abnormalities may sometimes be severe.

We thank the department of illustration, Birmingham Children's Hospital, Jacqueline Boaler for preparation of the manuscript, and Dr JC Clay for helpful discussion.

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# Post-streptococcal glomerulonephritis in Hong Kong

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SUMMARY Of 74 paediatric inpatients with acute glomerulonephritis, 58 (78%) had a raised (>1/200) antistreptolysin O titre. Serum C3 concentration was low in 73, but returned to normal within six weeks. Streptococcal infection remains the commonest cause of acute nephritis in children in Hong Kong, possibly due to overcrowded living conditions.

Over the past 20 years the incidence of acute glomerulonephritis in developed countries has fallen considerably, and the aetiological role of streptococcal infection seems also to have waned. Meadow in 1975 found that only one third of 43 children in Leeds with acute nephritis had had a recent streptococcal infection.[1]

The pattern of illness in children in Hong Kong is similar to that in other developed parts of the world,[2] yet it was thought that acute glomerulonephritis was more common than in Western countries. We therefore set up a prospective study to determine whether recent streptococcal infection remains a major cause of acute glomerulonephritis in these children.

## Patients and methods

From July 1984 to July 1986 we studied all children with acute glomerulonephritis admitted to two regional hospitals, one in Kowloon and the other in the New Territories. Criteria for diagnosis comprised gross or microscopic haematuria and at least two of the following: diastolic blood pressure of >80 mmHg, plasma urea concentration >6·6 mmol/l, oedema or oliguria.[1] Children with primary renal disorders were not included.

Seventy four children with suspected acute nephritis were studied: 43 boys and 31 girls, aged from 8 months to 15 years. Particular attention was taken of any throat, respiratory tract, or skin infections in the previous four weeks. We also asked if the children had seen a doctor before admission, and if they had received any medication. Throat swabs for culture and blood specimens for estimation of antistreptolysin O (ASO) titre and assay of C3 complement concentration in serum were taken within five days of admission. Throat swabs were placed in Stuart's transport medium before being sent to the laboratory for culture on blood agar in carbon dioxide. ASO titre was assayed using a modified microtechnique with a microtitre plate; a titre of >1/200 was considered to be diagnostic of streptococcal infection. Serum C3 complement was assayed by rate immunonephelometry using the Beckman ICS-II analyser and reagents. All children except 12 with acute nephritis had at least two samples of blood taken for measurement of ASO titre and C3 complement concentration within six weeks of admission.

Where possible we enrolled other children as controls. Sixty six control children were studied, having been matched for sex and age (within one year of an index case). These were children whose admission to hospital was within one week of a study case, who were not suffering from a renal complaint, but who required venepuncture as part of the management of their clinical problem. Each had serum ASO titre and C3 complement concentration determined, and a throat swab was taken for culture.

## Results

In 60 patients the chief complaint was swelling of the face, hands, or feet. In only eight was discolouration of the urine the chief symptom. One child presented with a convulsion due to hypertensive encephalopathy. In 36 there was a definite history of a recent throat infection; in 14 skin seemed to be the likely primary focus of infection. Forty nine patients had a diastolic blood pressure of >80 mmHg on admission. Ninety per cent of the children had consulted a doctor before admission, and over half had been given a broad spectrum antibiotic. All the children recovered in hospital.

ASO titres of >1/200 were found in 52 (70%) of the study patients on admission compared with 12 (18%) of controls. In a further six patients ASO titres that were <1/200 on admission rose to >1/200 or more within a month. Serum C3 complement concentrations were low in all but one of the study group on admission, with a mean (SD) value of 24 (15) mg/dl (normal range 60–180 mg/dl). Each second specimen of 62 paired blood samples had a C3 concentration higher than the one obtained on admission. Serum C3 complement concentrations gradually returned to normal by the sixth week in all children from whom samples were collected (62), with a mean (SD) value of 89 (23) mg/dl.

Group A β-haemolytic streptococci were isolated from cultures of 10 throat swabs taken from patients with acute nephritis and from six of the controls. We attribute the low recovery rate of organisms from the throat swab cultures to the widespread practice of prescribing broad spectrum antibiotics before admission to hospital. Treatment with antibiotics could also have delayed the rise of the ASO titre, reducing the sensitivity of this method for the diagnosis of preceding streptococcal infection.[3]

## Discussion

Streptococcal infection continues to be the commonest cause of acute glomerulonephritis in children in Hong Kong, as it is in other parts of south east Asia.[4] Of the 74 patients studied, we were able to prove a recent streptococcal infection (diagnosed by a high ASO titre of >1/200) in 58 (78%). A low serum C3 complement concentration within the first week of presentation is considered by some to be a more reliable test for post-streptococcal glomerulonephritis[5]; all but one of the 74 children fulfilled this criterion.

The importance of the β-haemolytic streptococcus as a cause of acute glomerulonephritis in our children contrasts with Meadow's experience in Leeds where only one third had post-streptococcal glomerulonephritis.[1] Environmental conditions in Hong Kong may partly explain these differences. Despite considerable improvement in living conditions the density in terms of number of people per unit area of living space is still much higher than in Western countries, encouraging spread of streptococcal infection. Paradoxically the other major streptococcal disease, rheumatic fever, has virtually disappeared from Hong Kong. This raises the possibility that the high incidence of post-streptococcal glomerulonephritis might also be related to the persistence of nephritogenic strains of β-haemolytic streptococci in Hong Kong. In the present study we did not determine the types of streptococci, and further studies are in progress to investigate this aspect.

We thank Professor DP Davies and Dr PLS Ip for allowing us to study their patients, and Miss Fanny Lau for preparing the manuscript

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# Cushing's disease and craniopharyngioma

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SUMMARY A 14 year old girl presented with growth failure and Cushing's disease. Histological examination confirmed a craniopharyngioma but failed to show that the tumour secreted adrenocorticotrophic hormone. We suggest that her Cushing's disease was caused by hypothalamic dysfunction associated with increased corticotrophin-releasing hormone secretion, secondary to the craniopharyngioma.

Craniopharyngiomas usually present with symptoms and signs of increased intracranial pressure or localising neurological signs, or both; some, however, present with failure of growth and puberty due to progressive loss of hypothalamic-pituitary function.[1] We describe a girl who had a craniopharyngioma and presented with the sequelae of pituitary hypersecretion of adrenocorticotrophic hormone (ACTH).

## Case report

A girl presented at the age of 14·2 years with short stature. Her height was 3·6 standard deviations below the mean for her age, and her skeletal maturation was retarded by two 'years' The normal consonance of growth and puberty had been lost and her growth rate was only 3 cm a year, although she had attained stage 2 breast development, this suggested an endocrine abnormality.[2] Investigation showed a normal female karyotype, normal thyroid function (serum thyroxine 144 nmol/l), and normal tomograms of the pituitary fossa The 0900 h plasma cortisol concentration was 540 nmol/l In response to insulin induced hypoglycaemia, plasma cortisol rose to a peak of 750 nmol/l and the serum growth hormone concentration increased from 3·4 to 21 mU/l (normal peak >20 mU/l).

At 15·3 years her diurnal plasma cortisol concentrations suggested loss of normal diurnal rhythm, with morning and midnight concentrations of 335 nmol/l and 225 nmol/l, respectively (range <120 nmol/l at midnight). These samples were, however, drawn during the first 24 hours in hospital and the results were attributed to stress.

At 16·3 years she had Cushingoid facies, hirsuties, increasing central obesity, spider naevi, and persistent growth failure. She was hypertensive with diastolic blood pressure consistently 90 mm Hg. She had no defects of her visual fields, even on testing with a red target. Plasma potassium concentration was at the lower limit of normal (3·5 mmol/l). The 0800 h plasma cortisol concentration was 731/nmol/l with a plasma ACTH concentration of 67 ng/l, and the midnight plasma cortisol concentration was raised at 580 nmol/l. In response to insulin induced hypoglycaemia the plasma cortisol concentration rose from 248 nmol/l to 483 nmol/l. An intravenous injection of 100 µg of corticotrophin releasing hormone-41 (CRF-41) produced a peak plasma concentration of ACTH of 107 ng/l after 15 minutes and a peak cortisol concentration of 1210 nmol/l after 60 minutes. An exaggerated response to CRF-41 is a recognised finding in pituitary-dependent Cushing's syndrome.[3] The basal prolactin concentration was normal at 145 mU/l. Basal serum androgen concentrations were raised for a girl at her stage of puberty (dehydroepiandrosterone

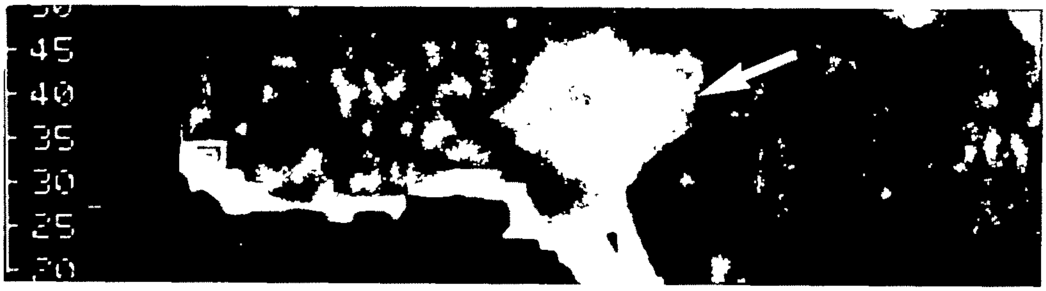

Figure *Sagittal reconstruction of enhanced computed tomogram through the centre of pituitary fossa showing a large suprasellar lesion [arrow] extending into the hypothalamus*

[DHA] 22·4 nmol/l, androstenedione 4·1 nmol/l, testosterone 2·4 nmol/l) but complete suppression of cortisol. DHA and androstenedione occurred after she was given 8 mg of dexamethasone orally each day for three days.

An abdominal ultrasound examination showed adrenal glands of normal size and morphology. A high resolution computed tomogram [GE9800] showed a suprasellar cystic lesion (figure). Following craniotomy this was resected, together with all residual pituitary tissue; histological examination confirmed a craniopharyngioma. There was no collection of basophilic cells suggestive of an adenoma, and no response to tumour tissue staining for ACTH, CRF, or bombesin After operation her Cushingoid signs resolved rapidly and she required full pituitary replacement with thyroxine, hydrocortisone, growth hormone, oestrogen, and deamino-D-arginine vasopressin During the year after the operation she grew 5 cm, and finally stopped growing at the age of 13. She has completed two years of follow up and has made an excellent recovery with no radiological evidence of residual tumour or biochemical recurrence of Cushing's syndrome.

## Discussion

This patient presented with loss of the normal harmony of growth and puberty, which usually indicates an endocrine abnormality. This allowed an early diagnosis of Cushing's syndrome before florid signs of hypercortisolaemia became apparent. The diagnosis was confirmed by loss of the normal diurnal rhythm of cortisol secretion. The plasma ACTH concentration, dexamethasone suppression test, and response to intravenous CRF-41 differentiated Cushing's disease from ectopic ACTH and primary adrenocortical hypersecretion. In addition, the histochemical studies of the tumour showed no evidence of ectopic hormone production. We can find no previously reported association between Cushing's disease and craniopharyngioma. The possibility of hypersecretion of ACTH caused by pressure from a non-functioning hypothalamic-pituitary tumour has, however, been suggested.[4] It is also possible that the hypersecretion may be due to release of inhibition rather than to direct stimulation.

There is controversy concerning the relative roles of the hypothalamus and the pituitary in the aetiology of Cushing's disease.[5] A primary role of the pituitary was unlikely in our patient as there was no histological evidence of a pituitary basophil adenoma. We suggest that hypothalamic dysfunction, caused by the craniopharyngioma, produced hypersecretion of ACTH secondary to increased secretion of CRF.

We thank Professor L Rees, Department of Biochemical Endocrinology, St Bartholomew's Hospital, London, for the histochemical tumour studies

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# Perioperative dissemination of salmonella

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SUMMARY A hypophyseal adenoma was operated on in a patient who was a carrier of *Salmonella typhimurium*. A chronic salmonella osteitis developed in her calvarium at the site of operation. Our case and reported experience emphasise that asymptomatic carriers of salmonella should be given perioperative antibiotic prophylaxis, especially if they are immunosuppressed.

The clinical presentation of salmonella infections is variable, particularly in patients having operations and cytotoxic treatment. Wolfe *et al* found that the risk of salmonella infection was high, particularly in patients with leukaemia and lymphoma.[1] *Salmonella typhimurium* and *Salmonella enteritidis* both cause bone and joint infections.[2]

In addition to having an increased risk of unusual complications associated with acute salmonella infections, carriers of salmonella receiving cytotoxic treatment should be regarded as having an additional preoperative risk factor. To emphasise this aspect of salmonella infection we report the case history of a girl with a hypophyseal adenoma who was operated on while she was a carrier of *S typhimurium*. A chronic salmonella osteitis developed in her calvarium at the site of operation.

## Case report

In September 1985 a 12 year old girl was referred to this department with a one week history of headache and right sided ptosis. Computed tomography was done, which showed changes consistent with a hypophyseal tumour. A few days before the onset of neurological symptoms she had had diarrhoea, as had other members of her family. Stool cultures from the patient and from other members of her family were positive for *S typhimurium*. A craniotomy was performed. At operation the tumour was found to be inoperable but a biopsy specimen was taken. Histological examination showed the presence of an hypophyseal adenoma. Dexamethasone was given to decrease intracranial pressure and anticonvulsant treatment using phenytoin was started postoperatively Three weeks after operation she had a course of radiotherapy. Recovery from the operation was uneventful without signs or symptoms of systemic or local infection.

Table *Timing and duration of drug treatment*

| *Drug* | *Days after operation that drug started* | *Duration of course* |
|---|---|---|
| Dexamethasone | −6 | 20 |
| Phenytoin | 0 | Continuous |
| Amphicillin (intravenously) | 39 | 5 |
| (orally) | 44 | 16 |
| Trimethoprim/sulphamethoxazole | 66 | 17 |
| Chloramphenicol (topically) | 74 | 18 |
| Trimethoprim/sulphamethoxazole | | |
| (orally) | 164 | 9 |
| (intravenously) | 173 | 16 |
| (orally) | 189 | 8 |

One week after the operation stool culture was still positive for *S typhimurium*, whereas the stool samples taken during the subsequent six months were all negative. Four weeks postoperatively inflammation, swelling, and a small fluctuant mass were noted at the surgical wound site. Needle aspiration was performed and *S typhimurium* cultured from the sample. The infection was unsuccessfully treated with several courses of antimicrobial drugs (table) to which the strain was sensitive on culture, the cultures from the wound remained positive.

Four and a half months after operation osteitic changes were seen on the skull *x*-ray picture and a further craniotomy performed. At operation it was found that the bone which in the primary operation had been transplanted to the calvarium from the iliac crest was infected. The infected piece of bone was removed. Before the second operation oral trimethoprim-sulphamethoxazole was given, and this was continued intravenously for 16 days after operation and then for a further eight days orally. After the second operation the wound healed, and no residual infection was detected during the 10 month follow up.

## Discussion

There is a wide variety of complications of infections caused by any strain of salmonella.[2 3] The possibility of the development of bone infection in an asymptomatic carrier is not, however, well recognised. Gilman *et al* found that bone marrow is a more sensitive culture medium for *Salmonella typhi* than stool, blood, or urine in patients with typhoid fever.[4] The reason for our patient developing bone infection may be due to the ability of salmonellas to invade bone marrow. If this is the case then the bacteria were actually in the bone marrow at the time of the primary operation. Another possibility is that occult bacteraemia may have occurred during the early postoperative period when the patient was still carrying salmonella. Young patients with positive blood cultures may be asymptomatic.[5]

The first sample from which *S typhimurium* was cultured was taken by aseptic needle aspiration. The stool cultures had been negative for three weeks before signs of the infection at the operation site were detected which makes faecal contamination of the wound an unlikely source of infection. Our case corroborates the fact that salmonellas tend to infect diseased or injured tissue. The use of radiotherapy in conjunction with dexamethasone probably increased the likelihood of salmonella causing the infection.

Rodriguez *et al* recently published a review of intracranial infections caused by salmonellas.[6] In their report one patient developed a focal salmonella infection in a neoplastic lesion within the central nervous system. Our patient did not have any symptoms or signs of intracranial infection, and was cured after the removal of the infected bone.

Our case shows that even an asymptomatic salmonella carrier should be given prophylaxis when any surgical operation is planned Chloramphenicol or trimethoprim-sulphamethoxazole should be given before, during, and after the operation to prevent local complications. There is, however, no curative treatment for the salmonella carrier, and antimicrobial treatment may prolong carriage. The use of bone marrow culture for salmonella is a useful diagnostic sampling medium

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# British Paediatric Association

## Minutes of the Annual General Meeting

**The Annual General Meeting of the British Paediatric Association was held on 8 April, 1987 in the Central Hall of the University of York. The President, Professor J O Forfar, took the chair.**

### 1 APOLOGIES

Apologies for absence were received from Professor Barbara Clayton.

### 2 MINUTES OF THE 1986 ANNUAL GENERAL MEETING

The minutes of the meeting held on 16 April 1986, which had been circulated to members in March in the Annual Report, were accepted and signed as a correct record

### 3 PRESIDENTIAL ELECTION

The meeting noted the election of Professor June Lloyd as President-Elect 1987–88 and President 1988–91.

### 4 ELECTION OF HONORARY OFFICERS

The meeting ratified Council's election of Dr T L Chambers to serve as Honorary Secretary and Dr R W I Cooke and Dr Marion Miles to serve as Honorary Assistant Secretaries 1987–89.

### 5 PRESIDENT'S REPORT

The President's Report had been circulated to members in March in the Annual Report and was APPROVED by the Annual General Meeting.

The meeting stood in memory of the members who had died since the last meeting: Dr B Chown (Honorary Member); Dr Christine Cooper (Honorary Member); Dr E W Hart (Honorary Member and former Honorary Secretary to the Association); Dr D MacCarthy (Honorary Member); Dr D Pickering; Sir Harry Platt (Honorary Member); Sir Desmond Pond (Honorary Member)

The President referred to the Association's recently published reports on 'The School Health Service', 'Paediatric Training in the United Kingdom', and 'Paediatric Intensive Care'. Copies of these reports were available from the BPA office.

The Association was being consulted increasingly as it became recognised that the BPA was the appropriate body to consult on paediatric matters.

A document on the 'Integration of the Child Health Services had been agreed by the BMA Child Health Forum and unanimously approved by the BMA Council. The President thanked the Honorary Treasurer for his contribution to these discussions.

Professor S R Meadow was retiring as editor of the Archives of Disease in Childhood. On behalf of the Association, the President thanked Professor Meadow for his assiduous service over the past seven years.

The President thanked the Executive Secretary and the other members of the secretariat for their hard work and valuable contribution to the work of the Association.

### 6 ELECTION OF NEW MEMBERS

Professor Barbara Clayton, Professor J Dobbing, Dr Patricia Ryan, Sir Peter Tizard, Dr C H M Walker, Professor O C Ward and Dr B W Webb had been proposed for Honorary Membership and there were nominations for one hundred and twenty one Ordinary Members, twelve Overseas Members and fifty six Associate Members. The meeting approved the nominations and the new members were duly elected.

### 7 TREASURER'S REPORT

The Treasurer presented the Accounts for the period 1 January to 31 December 1986. These had been circulated to members with the Annual Report and had subsequently been audited. There had been a surplus for the year and a substantial sum had been transferred to reserves. According to agreed financial policy, the Association's activities continued to be funded by income from members' subscriptions and investments and the contribution from the trade exhibition. Profits from sales of the Archives of Disease in Childhood had been used to build up the Association's reserves. The cost of the journal had now been fixed in sterling, so that profits would be lower than in previous years but the level of income from this source would be more predictable in future. The Association had taken expert advice on the management of its investments on which maximum return had been obtained. An increase in expenditure during the year reflected the growing activities of the Association and the consequently higher demand for administrative support.

The Association was advised that its trading activities had increased to the point where it would be necessary to register for VAT. A public limited company, British Paediatric Services Ltd was being formed to undertake those aspects of the Association's work which would be liable to VAT.

The Honorary Treasurer thanked Mr Michael Ray, the Association's financial adviser, and the secretariat for their work in preparing the accounts.

The Honorary Treasurer's verbal report and the circulated Accounts for 1986 were APPROVED.

### 8 MEMBERS' SUBSCRIPTIONS

The meeting agreed that the annual subscription rate for Ordinary Members should be increased to £98 from 1 January 1988, with pro rata increases for lesser rates.

### 9 APPOINTMENT OF AUDITORS

The meeting appointed Messrs Arthur G Mead & Co as auditors for the financial year 1986–87.

### 10 RULES OF THE ASSOCIATION

The meeting considered amendments to the Rules of the Association which had been circulated to members in March in the Annual Report Proposed amendments to Rule 2 MEMBERSHIP 2b Election of Members were accepted.

### 11 REPORT OF THE ACADEMIC BOARD

The Report of the Academic Board which had been circulated to members in March in the Annual Report was received. The President expressed the Association's gratitude to Professor J D Baum for his valuable service both as Secretary to and Chairman of the Academic Board.

### 12 REPORTS FROM PAEDIATRIC SPECIALTY GROUPS, STANDING COMMITTEES, WORKING PARTIES, AND OUTSIDE BODIES

The meeting received reports which had been circulated in the Annual Report to members in March. The President thanked all those who had served and contributed to this important aspect of the Association's work.

### 13 THE FUTURE REPRESENTATION OF PAEDIATRICS

There was extensive discussion on Council's proposals that steps should be taken towards changing the professional representation of paediatrics and child health in the UK.

Council had submitted the following resolutions to the AGM.

a) This Annual General Meeting endorses Council's recommendations to approve the following objectives to be achieved by the future representative body for paediatrics and child health:

1. Greater professional recognition of the importance of children and improved status of paediatrics and child health.
2. Responsibility for setting and maintaining standards of practice in child health and paediatrics and its specialties in the UK
3. The right, recognised by the Royal Colleges of Physicians and endorsed by the other Royal Colleges and Faculties, to speak for paediatrics and child health as the authoritative voice of these disciplines and to represent them at national and regional levels.
4. Representation on committees and councils on which paediatricians feel they should be represented, including the right to elect their own representatives who would be recognised as representing paediatrics and child health.
5. Maintenance of the right to publish reports and statements without prior endorsement by other bodies.
6. Responsibility for postgraduate examinations and for training in paediatrics and child health.
7. The right to appoint regional paediatric advisers who would be the recognised source of advice for health authorities on, inter alia, matters concerning career and training posts in paediatrics and child health.
8. Adoption of general structure (including paediatric specialty groups), organisation and constitutional aims similar to those of the British Paediatric Association.
9. As the body representing paediatrics it would be responsible for formulating advice on paediatrics and child health and would replace the Joint Paediatric Committee of the Royal Colleges of Physicians of the UK and the BPA and the Paediatric Committees of the Royal Colleges of Physicians.
10. Arrangements for finance and accommodation acceptable to the members of the future representative body.

Professor R W Smithells proposed and Professor June Lloyd seconded an amendment deleting the words 'recognised by the Royal Colleges of Physicians and endorsed by the other Royal Colleges and Faculties' from Objective 3.

Voting was 116 for and 43 against the amendment. Amended Resolution a) was then adopted unanimously.

b) This Annual General Meeting authorises Council to hold a referendum to determine
   i) whether the membership wishes to change the present representation of paediatrics in the UK and
   ii) whether this should be better achieved through the formation of a Faculty within the Royal Colleges of Physicians or through a separate and independent College of Paediatricians.

Professor O H Wolff proposed and Professor F Harris seconded a resolution inserting a third clause iii) 'Voting in the referendum should be by single transferable vote on the three options: preserving the status quo, forming a Faculty of the Royal Colleges of Physicians and forming an independent College' Voting on the amendment was 117 for and 2 against.

The amended Resolution b) was then adopted unanimously.

c) This Annual General Meeting endorses Council's recommendation that voting in the referendum will be confined to the Ordinary members of the Association.

Professor S R Meadow proposed that the words 'and the full results of the referendum should be made available to the membership of the Association' be added to clause c).

The amendment was accepted by the President and the amended resolution was adopted unanimously.

d) This Annual General Meeting empowers Council to negotiate the achievement of the Objectives enumerated in Resolution a) taking into account the result of the Referendum.

It was proposed that the following words be added: 'the results of the negotiations to be brought back to the Annual General Meeting in 1988, and thereafter to be the subject of a further referendum'.

This proposal was accepted and the amended resolution carried by 130 votes to 3.

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# Correspondence

## Trends in birth prevalence of cerebral palsy

Sir,

The paper by Pharoah *et al*[1] is a splendid example of the confusion that can arise when a perinatal problem is examined only through the eyes of a paediatrician I am prepared to concede that a rise in the incidence of cerebral palsy in low birthweight (LBW) infants before 1977 exonerates intensive care as a cause. But the implication that it lets paediatricians off the hook does not necessarily follow

Firstly, I think I speak for both perinatal pathologists and ultrasonographers when I say that the diagnosis of brain damage as a cause of cerebral palsy is comparatively rare before birth, but becomes increasingly easier postnatally For those who believe that anatomy is related to function most cases of cerebral palsy appear to have their origins intrapartum and especially in the immediate postpartum period

Secondly, and here I speak on behalf of obstetricians, the phenomenon of a rising rate of cerebral palsy in LBW infants cannot be understood without knowing the stillbirth rate in LBW infants during the same period The authors' figures show a declining birth rate (45 637 to 28 430 from 1966–77) which is unlikely to be due entirely to a declining population. At the same time there was a declining risk of LBW at least among live births and hypothetically also among stillbirths. In 1967 there were 68·2 live births below 2500 g per 1000 births, rising to a peak of 79·8 in 1970 and thereafter reducing to 50·8 per 1000 births in 1977 An obstetrician could be expected to interpret this as reflecting improved living standards, family planning, and more successful antenatal obstetric care This is difficult to reconcile with an increasing risk of being deprived of oxygen during and after birth. I suspect that immediately before the dawn of intensive care for the newborn, growing enthusiasm for relatively unsophisticated resuscitation of small babies provoked the significant rise in the incidence of cerebral palsy as well as an increased chance of survival. From the authors' figures survival below 1500 g rose from 33% to 49% and for infants between 1500 and 2500 g from 94% to 97% for the period 1967–1977

On the other hand, without knowing how many LBW infants were stillborn it could be argued that the propensity of the Merseyside mother to go into premature labour remained unchanged between 1966 and 1977 A rising stillbirth rate in LBW infants would then necessarily be accompanied by the recorded decline in LBW live births In this case the blame would lie more at the obstetrician's than the paediatrician's door, because the fewer liveborn infants who escaped the increasing risk of death in utero would be more likely to be hypoxic at birth and more at risk of cerebral palsy

There is ample evidence that modern obstetric practice and neonatal intensive care have simultaneously had repercussions for each other[2] Cerebral palsy is unlikely to have been independent of either of these disciplines before the institution of intensive care. The traditional plea of the community paediatrician to examine 'geographically delineated groups' must be challenged. The study of a disease in a community is justified when (as is usual) the disease has its origins there. This would be acceptable for a study of congenital malformations but not for cerebral palsy Most infants with cerebral palsy have been admitted to a maternity hospital with a morphologically normal central nervous system whilst in utero, and are subsequently discharged to the community with pathological cavities in their brains Hospital based figures make sense for cerebral palsy as the disease originates within its walls Geographically delineated groups merely average the results of differing hospital practices.

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Professor Pharoah and Drs Cooke, Rosenbloom, and Cooke comment:

In his criticism of our paper, Barson makes several points that are unsubstantiated by any evidence The first is that the diagnosis of brain damage as a cause of cerebral palsy is rare before birth but becomes increasingly easier postnatally. This may be so, but that cannot be translated to mean that *most* cases of cerebral palsy appear to have their origins either intrapartum or, more especially, immediately post partum. Merely being unable to diagnose brain damage with currently available techniques, including ultrasound, does not mean that abnormality is not already present Indeed, all the evidence refutes this view and indicates that in most cases of cerebral palsy brain damage occurs well before labour begins In the cohort followed up by Nelson *et al* only 9% of cases were damaged perinatally.[1] Even among low birthweight (LBW) infants, Stewart *et al* found that 52 of 68 infants with neurodevelopment disorders had no periventricular haemorrhage or parenchymal densities or had only a small periventricular haemorrhage.[2]

In answer to Barson's second point, national data reveal that the stillbirth rates for LBW babies are also falling.[3] In the Mersey Region similar data are not available for the period before 1974, but from 1974 to 1977 the pattern of decline in stillbirth rates followed the national one There is, therefore, no evidence that the decline in early neonatal mortality was achieved at the expense of a rise in stillbirth rate

The final point is that hospital rather than geographically delineated groups should be studied on the basis that the causative factors for cerebral palsy originate within the hospitals This is emphatically not so, it must be restated that for most cases, even those of LBW, cerebral damage occurs well before birth. To use Barson's phraseology, this lets both obstetricians and paediatricians off the hook, but it behoves all of us to seek the nature and timing of the insult(s) which compromise cerebral development *Pace* Barson, observing a hospital population cannot account for the biases inherent in differential inter hospital transfer rates and clinical management policies which may affect prevalence without any bearing on the incidence of the condition

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# Prediction and management of nocturnal hypoglycaemia in diabetes

Sir,

Following the report of Whincup *et al*[1] I have analysed my own data on hospital based blood sugar profiles with rather different results

A group of 118 diabetic children were admitted to the Royal Manchester Children's Hospital for 24 hours for a study of their renal function.[2] Capillary blood was taken before and one hour after meals and at 0300 hours for estimation of plasma glucose concentrations. In 107 of these children an after supper (usually 2100 to 2300 hours), and 0300 hour plasma glucose estimation were available for predictive analysis Nocturnal hypoglycaemia was defined as a plasma glucose concentration of less than 3 mmol/l. The table shows the results.

Table *Predictive value models for nocturnal hypoglycaemia (n=107)*

| *Plasma glucose concentration after supper (mmol/l)* | *Sensitivity* | *Specificity* | *Predictive value* | |
|---|---|---|---|---|
| | | | *Positive* | *Negative* |
| <4 | 25 | 97 | 40 | 94 |
| <5 | 50 | 91 | 31 | 96 |
| <6 | 50 | 85 | 22 | 95 |
| <7 | 63 | 78 | 19 | 96 |
| <8 | 63 | 72 | 18 | 97 |
| <9 | 63 | 65 | 15 | 97 |
| <10 | 63 | 63 | 14 | 97 |

Twenty seven children had a plasma glucose concentration <7 mmol/l after supper and of these only five had one of <3 mmol/l at 0300 hours. Eighty children had a plasma glucose concentration >7 mmol/l after supper and of these three had one of <3 mmol/l at 0300 hours. Thus for these data the after supper plasma glucose value was a poor predictor of nocturnal hypoglycaemia, being correct only about one fifth of the time.

I suspect that the difference between these results and those of Whincup *et al* reflects a difference in the per cent of the two populations that were confirmed positive and confirmed negative The predictive value of a test depends entirely upon the ratio of confirmed positive and confirmed negative results in the population.[3] In this data set, 7·4% of the population were confirmed positive compared with the 34% of that of Whincup *et al* I can only speculate on what percentage of the general population of diabetic children have nocturnal hypoglycaemia, but from clinical practice I would be surprised if it was more than 10% to 20%.

There is an additional problem with predictive analysis Feinstein comments that such an analysis has to accept the idea that the results can be listed in a fourfold table.[3] Thus the presence of 'nocturnal hypoglycaemia' is expressed as a simple 'yes' or 'no' and the results of the after supper plasma glucose estimations are similarly interpreted. This is a simplification of the realities of glycaemic control and of home blood glucose monitoring in diabetic children, where the results are rarely 'yes' or 'no' but often 'perhaps' or 'maybe'

Most British paediatricians ask their diabetic children to perform one blood glucose test at home at a different time each day Acceptance of this predictive model implies two home blood glucose tests each day; one during the course of the day and one at bedtime. Personally I find it difficult establishing a once daily home blood glucose monitoring routine for most diabetic children and I believe that, for many, a twice daily routine would be difficult to achieve.

In conclusion, therefore, despite the results of the intervention study I remain unconvinced by the argument that paediatricians should be encouraging some of their diabetic children to estimate a nocturnal blood glucose concentration to reduce the incidence of nocturnal hypoglycaemia.

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# Baby walkers . . . time to take a stand?

Sir,

I agree with the report of Gleadhill *et al* on the dangers of baby walkers.[1] I think, however, that the fact that two of the three cases they describe involved infants no older than 7 months who were left unsupervised in these baby walkers indicates that there was insufficient parental care. This would certainly appear to be so at the time of the accidents. Placing a young infant in a baby walker and thus giving him uncontrollable speed and mobility without supervision is as irresponsible as allowing a [illegible] year old to drive a motor car

My experience is that those parents who are somewhat inadequate, depressed, or socially deprived are among the most ardent users of baby walkers. The infant is placed in this and then left to 'amuse' himself. These parents often have little insight into normal child development and are unprepared for the consequences of the mobility suddenly achieved by the infant

Another factor is that it is usually the infant who is irritable and hyperactive who is most often placed in a baby walker. The combination of a hypractive adventurous infant and an insufficiently observant parent is also found in other cases of accidental injuries and poisoning [2] Education and warning labels may help but unfortunately these are often the families who are least amenable to advice on child care and safety.[3] Even if the baby walker complies with the strictest safety regulations accidents will still occur—especially from overturning The total banning of the sale of baby walkers may be the only resort if these accidents are to be prevented completely

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Sir,

I share the concern about the safety of baby walkers, expressed by Gleadhill *et al* [1]

The susceptibility of infants in baby walkers to burns was pointed out by Colville and his colleagues in Belfast,[2 3] who reported 31 severe burns over a decade, showing the hazards to which babies were being exposed

Our own data confirm the conclusions of Gleadhill *et al* that these devices are still a source of serious injury, even after strenuous efforts by the British Standards Institute and by public information campaigns. Of 160 burns severe enough to merit admission to the Leicester Royal Infirmary Burns Unit over the last year, 3 (1·9%) were associated with the use of baby walkers. This represents 22·2% of children of baby walker age (8 to 14 months). Of 400 sequential burns over the last six months requiring outpatient treatment, however, none was connected with baby walkers

Thus not only are these devices still causing burns, but the kind of burns they cause to a child robbed of his normal protective reflexes by these 'mobile straight jackets' are generally of a serious nature I therefore agree that it is indeed 'time to take a stand' on the use of the baby walker device.

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# Vasoactivity of the major intracranial arteries in newborn infants

Sir,

We read with interest the paper by Drayton and Skidmore[1] but suggest that their conclusions cannot be justified by the data provided in their paper. The statement that the major cerebral arteries are the main site of autoregulation is based entirely on the observation that there is no change in the cerebral blood flow (CBF) as measured by their Doppler method We are not convinced that the method they used is valid and appropriate to the measurement of CBF

Absolute flow is difficult to measure accurately using Doppler ultrasound.[2] The method used by Drayton and Skidmore is particularly inaccurate as small errors in the measurement of flow made at two points will lead to large errors in the calculated differences, although the two flow estimates are subtracted, the error is additive. Even under ideal conditions (a non-reactive circular aorta) accuracy of measurement of the aorta cannot be better than the order of a wavelength of ultrasound and will lead to an error of about 6% when measuring the diameter of the immature aorta (about 8 mm) and a 12% error in a cross sectional area. We calculate that for an infant weighing 1500 g where about 30% of the flow in the ascending aorta perfuses the head and arms and 80% of this perfuses the brain, then the smallest likely error in calculating the flow to the upper part of the body by the subtraction method is of the order of 50% Details of these calculations are available on request to us Our calculations are based on four assumptions: a closed ductus arteriosus, a brain weight of 150 g, CBF of 60 ml/100 g/minute,[1] and a cardiac output of 260 ml/minute/kg.[3]

There is a great deal of evidence to support the contention that regulation of CBF is mediated by the microvasculature. Drayton and Skidmore have, however, chosen to ignore these data in suggesting that the major cerebral arteries perform the main role in regulating blood flow. We do not disagree that in mature animals (and possibly humans) the major cerebral arteries may show vasoactivity in response to changing patterns of flow, but we can find no data from the work of Drayton and Skidmore to support this assertion in the premature infant. The onus is on them to show that their method for measuring CBF correlates with any other independent method either in humans or in animals before we can accept that major cerebral arteries mediate cerebral autoregulation in the preterm neonate

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Drs Drayton and Skidmore comment

Our finding of a large increase in cerebral artery blood velocity during the first 48 hours of life but no change in a measure of cerebral blood flow (CBF) has important implications for simpler Doppler techniques of assessing the cerebral circulation Levene *et al* question whether limitations of our volumetric technique could explain the absence of any apparent increase in CBF

It is true that if there had been progressive and unidentified constriction of the aortic isthmus over the 48 hours, CBF might indeed have risen We know of only two detailed studies of sequential changes in the size of the isthmus both of which conclude that there is a progressive but slow relative increase in the diameter of the isthmus from birth [1 2] The isthmus has a different embryological origin from the ductus arteriosus, and is histologically indistinguishable from the rest of the aortic arch, which decreases the likelihood that it constricts in a similar manner to the ductus itself.[3] M mode measurement of the diameter of the isthmus in our infants was frequently impossible but measurements from the real time image did not suggest that there were any progressive changes in diameter over the time course of our studies The oval section of the aortic isthmus may introduce a small but constant error in our calculations but this is irrelevant to this discussion of change in velocity and flow

In our opinion the basis for their calculation of potential error in our technique is inappropriate. Our own calculations, available from us on request, give a potential error in mean CBF of 9% for the preterm group and 16% for the term group, both well below the percentage change observed in cerebral artery velocity

We may approach the same problem empirically by using the dispersion in our data that incorporates error and variation from all sources to calculate the confidence limits for any change We can thus be 95% certain that any change in CBF between 1·5 and 48 hours was between +32% and −30% for the preterm group and +28% and −33% for the term group

Levene *et al* conclude from the work of Kennedy *et al* that there is an increase in CBF in the first few days of life in dogs born at term Their results, however, showed no increase in CBF over the first six days of life. Furthermore, Cooke *et al*, using venous occlusion plethysmography in the term human infant, showed quite clearly that CBF was constant between three and 24 hours and that in fact flow was rather higher during the first two hours.[4]

Contrary to the statement of Levene *et al*, nowhere in our paper have we suggested that 'the major cerebral arteries perform the main role in regulating blood flow' Clearly in the normal brain perfusion is closely coupled to metabolic demand in the tissues and important local mechanisms regulating flow must exist We do contend that the regulation of CBF is unusual in occurring at more than one arterial level including the major cerebral arteries The quoted work of Ahmann *et al* suggests that in the anterior cerebral arteries of only three preterm infants studied the vessels had an immature muscle coat, whereas in eight infants of a wide range of gestations studied by ourselves the muscle wall was well developed It seems illogical that Levene *et al* are prepared to accept that the major cerebral arteries of mature animals and humans are vasoactive, but are unwilling to accept the same for neonates. Our technique has been carefully validated in vitro Appropriate animal models for validation in vivo are not currently available to us and we do not believe that acceptable gold standards for the measurement of CBF in the newborn human exist. We believe that investigators who rely on the use of mean cerebral artery blood velocity as a measure of CBF may be misled

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## Interaction between chloramphenicol and acetaminophen

Sir,

Dr Choonara[1] raises the possibility that the changes in chloramphenicol pharmacokinetics observed in our study[2] were unrelated to acetaminophen

The pharmacokinetics of chloramphenicol could be influenced by many factors including age, underlying disease, degree of hydration, fever, and other drugs Study designs and data analyses controlling for all these variables are difficult and sometimes impossible in very sick patients The studies of Nahata *et al*[3] and Toumanen *et al*[4] included many patients with these confounding variables. Nahata *et al* studied 10 children with infection of the central nervous system, four of whom received phenobarbital or phenytoin, or both; these are both known to induce hepatic enzymes. One child also received acetaminophen Toumanen *et al*[4] studied 44 children with bacterial meningitis, 11 of whom had seizures requiring anticonvulsants All 44 children were feverish (38·5 to 41°C). In contrast, four of our five patients had epiglottitis, an illness of rapid onset and short duration. They had previously been in good health and had not received any medication before presenting with breathing difficulty. When studied 48–72 hours after chloramphenicol had been started, all five were well hydrated and only one was feverish (38·1°C) Nahata *et al*[3] reported an increase in chloramphenicol and chloramphenicol succinate kinetics in their 10 children. The mean area under the curve (mg/l/hour) and plasma half life t 1/2 (hours) for their patients when first studied were similar to those in our patients (105·7 and 3·0 compared with 112·2 and 3 0) These authors repeated their kinetic studies two to 17 days after the first and found that the mean area under the curve and t 1/2 had decreased to 79·5 and 2·3, respectively, compared with 28·7 and 1 2 in our patients (48–72 hours after the first study) They found that patients who had the greatest area under the curve at the time of the first study had the greatest decline We found no such correlation The mean (SD) change in the area under the curve among our patients was 74·1 (6·9)%, the patient with the smallest initial area under the curve had a 77·7% change and the patient with the largest had a 73·5% change

It is possible that the changes we observed in chloramphenicol pharmacokinetics were independent of acetaminophen. We agree with Dr Choonara that information on the pharmacokinetics of chloramphenicol after acetaminophen therapy or the use of control patients who concurrently received acetaminophen and chloramphenicol followed by chloramphenicol alone would have been ideal Hepatic microsomal enzyme activation may take days to weeks to return to the preactivated level after withdrawal of the inducing agent[5] The decrease in the urinary excretion of free chloramphenicol with an inverse relative increase in the glucuronide conjugate, and the magnitude of change in the kinetic profile of the drug in our patients who were studied on two occasions with 72 hours allowed us to conclude that a chloramphenicol-acetaminophen interaction existed as we had no other clear explanation for these changes Our conclusion also remains that therapeutic drug monitoring is necessary whenever drugs with a narrow therapeutic index such as chloramphenicol are used.

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# Neonatal typhoid fever

Sir,

In a recent article, Chin *et al* concluded that 'infants with mild *Salmonella typhi* enteritis do not require (antibiotic) treatment'[1] Diarrhoea is a common feature of typhoid fever in children, but is rarely associated with fluid depletion.[2] It should not, however, be inferred that the finding of *S typhi* in a stool culture is of no clinical importance; a positive stool culture, even in a healthy contact, is often followed by a typical septicaemic illness sever to 10 days later[3] Typhoid fever is usually a milder disease in children than in adults, but life threatening complications and even deaths have been reported, especially among young, malnourished infants.[3] The use of antibiotics has resulted in a considerable reduction in the morbidity and mortality of typhoid fever;[3] thus treatment of all cases of acute *S typhi* infections seems to be indicated.

According to Chin *et al* the duration of the carrier state of *S typhi* is not shortened by treatment with antibiotics In addition, chloramphenicol probably does not shorten the carriage time of *S typhi* in treated patients[3] The problem is that the reference cited by Chin *et al* to support this statement is not relevant The study mentioned was carried out among children suffering from uncomplicated, non-bacteraemic gastroenteritis caused by salmonella strains other than *typhi* and *paratyphi*, an entity totally different from typhoid fever.[4]

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Dr Chin and Dr Tarlow comment:

We thank Dr Yagupsky for his interest in our article. We did not imply that the finding of *S typhi* in a stool culture should be ignored. This is a potential health hazard as was pointed out in our paper. Typhoid fever can indeed be a life threatening condition as exemplified by our first case. We agree that the introduction of antibiotic treatment has reduced the mortality of typhoid fever. We do not, however, feel that all infants (including those with minimal gastrointestinal symptoms) require oral antibiotics. Although a septicaemic infection may occur later in some patients with mild symptoms, antibiotic treatment does not completely prevent a major clinical relapse after treatment has been stopped. It is not our policy to treat all healthy contacts, even if their stool cultures are positive.

Although the paper by Nelson *et al*[4] did not refer specifically to the use of antibiotics in *S typhi* infection, the randomised prospective double blind study did show that oral antibiotics were of no benefit to infants and children with acute salmonella gastroenteritis.[1] Furthermore, the treated patients had an increased risk of symptomatic relapse. We are not aware of any recent or similar study relating to *S typhi* gastroenteritis. Lastly, one must not forget that non-typhoid salmonella infections can also cause serious complications in infants.

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## Incidences of childhood coeliac disease and transient gluten intolerance move discrepantly in UK and Sweden

Sir,

Current criteria for the diagnosis of childhood coeliac disease were formulated by the European Society for Paediatric Gastroenterology and Nutrition. Coeliac disease was defined as a lifelong disorder in which the small intestinal mucosa is abnormal as a result of exposure to gluten in the diet. The mucosal damage improves on treatment with a gluten free diet but recurs within two years of reintroduction of gluten. In some cases, however, this gluten challenge does not bring about a mucosal relapse within the two year period. These children have so called transient gluten intolerance. In an earlier study we reported an incidence of transient gluten intolerance of 19% among children with an initial flat small intestinal mucosa that resembled that seen in coeliac disease.[1]

Since 1975 the incidence of coeliac disease seems to have decreased sharply in the UK[2] while the high incidence in Sweden has remained unchanged. On the other hand, we have observed a steep decline in the number of children with transient gluten intolerance diagnosed during the same period. This is in accordance with the findings of Walker-Smith who reported no new cases of transient gluten intolerance in children born after 1975 at the Queen Elizabeth Hospital for Children.[3]

The fact that the incidences of childhood coeliac disease and transient gluten intolerance are moving discrepantly in the United Kingdom and Sweden is interesting but puzzling, and suggests that factors other than gluten ingestion are involved in the pathogenesis of coeliac disease.

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*Archives of Disease in Childhood*, 1987, **62**, 1090–1092

# Book reviews

**Advances in Pediatrics. Volume 33.** Edited by LA Barness. Pp 415: £48·00 hardback. Year Book Medical Publishers Inc, 1986.

This book covers a series of diverse topics in which the editors feel there have been rapid changes in clinical and scientific areas of paediatrics. The result is 15 chapters of varying length, quality, and intensity ranging from the more esoteric 'dietary influences on neurotransmission' to the more down to earth 'α fetoprotein screening'. The chapters vary in their usefulness to the practicing paediatrician, necessarily having a North American bent, and on the whole do not yield easy answers to immediate practical questions.

Some chapters—for example those on cystinosis and chlamydial infections—are each a tour de force on the subject, and give historical reviews as well as full updates. There is a useful chapter on 'human teratogenicity' with balanced comment on the interpretative difficulties of animal studies, lists of established teratogens, and reference to up to date sources of information. The chapter on imaging procedures, by comparison, is low key with scant mention of the importance of antenatal ultrasound to paediatric practice, and no mention of the major advances in cardiac ultrasound. Other areas covered include 'vitamin E in neonatology', 'epilepsy and education', and 'inherited metabolic disease in the newborn'.

I am not convinced that the editors succeed in their aim to give us 'a refresher course in excitement'. They do, however, provide a useful book that deserves a place on our shelves to dip in to or for reference, but it is not light reading.

C S NELSON

**From Birth to Five. A Study of the Health and Behaviour of Britain's Five Year Olds.** Edited by NR Butler and J Golding. Pp 439: £24·95/$37·50 hardback, £14·95/$22·59 softback. Pergamon Press, 1986.

This impressive book distils the data obtained from a study of a national birth cohort. Many of the common childhood ailments and behaviour problems are included, with the addition of important chapters about the uptake and use of preventive health services. Sources of possible bias in the data collection are fully discussed and most results are illustrated by bar charts. Associations between variables are clarified by a statistical technique, indirect standardisation, and expressed in terms of relative risk. Each chapter is a model of clarity and ends with a succinct summary of the conclusions.

This is not a dry statistical exercise; if the authors find conclusions distressing or disturbing, they tell us so. Those seeking ammunition with which to continue the assault on social inequalities in health will find more than enough here, but with clear guidance as to the reliability of each conclusion. For example, once the data were standardised for maternal smoking and ethnic group, the association between low birth weight and social class disappeared. Regional variations are explored: can it be that babies in the south east of England cried more, when they were in most respects more privileged than their peers in the rest of the country? Behaviour is in the eye of the beholder, a point not avoided by the authors.

The only criticism is that most of the children studied were leaving school by the time the book was published, and some will by now be starting their own families. Although we are a decade adrift, the book is an invaluable reference for anyone concerned with the health of British children. The editors and their team have produced a cohesive and comprehensive work which is a tribute not only to them, but to the health visitors and mothers who made it possible.

D B CUNDALL

**Investigating Hearing in Children.** By L Fisch. Pp 273: £27·50 hardback. Croom Helm Ltd, 1987.

*Investigating Hearing in Children* is a readable book with an emphasis on the practical aspects of assessment. The author describes techniques suited to testing the hearing of children of all ages and gives advice on the construction of premises suitable for this purpose.

Dr Fisch's sympathetic understanding of young children is very evident in the techniques he describes in great detail in his book. I well remember visiting h assessment clinic some years ago and bei impressed by his kindly approach to th children. He describes the physics of sour and hearing in an easily understandab manner.

Some of the techniques which hav obviously served Dr Fisch well over th years have not worked too well for m personally. I have not, for example, bee very successful in testing hearing for spee at six metres; I felt that I had ofte dropped out of the child's world at th distance. Dr Fisch's relative scepticism f complicated electronic gadgetry—the aud tory response cradle, BSER, and mo recently ECochG—is a breath of fresh ai He obviously feels that we have n reached the stage where a machine can b considered to be more reliable than pai staking careful observation of behaviour responses to a range of sound stimuli. H regards results of electronic tests as suppo tive or otherwise of more simple te results, but certainly not as infallible! would recommend this book to communi health doctors, general practitioners ar paediatricians.

M YATI

**Atlas of Fetal Sectional Anatomy Wit Ultrasound and Magnetic Resonance Ima ing.** By G Isaacson, MC Mintz, ES Creli Pp 184: DM 228 hardback. Spring Verlag, 1986.

The aim of this book is to provide anat mical references for ultrasound and nucle magnetic resonance images of the fetu This is achieved by placing photographs gross anatomical sections alongside ultr sound images obtained from the fetus utero and nuclear magnetic resonance im ages obtained on aborted fetuses. For eac anatomical section there is also a detaile labelled diagram provided. The hea neck, thorax, and abdomen are shown various sagittal, coronal, and axial se tions, and there are separate chapte dealing with the limbs, the brain, and th heart. The majority of the scans feature 20 week fetus, but some show 24 week, week, 34 week, and 38 week fetuses. Th quality of the photographed anatomic sections is very good and the accompanyi belled diagrams are clear. The quality of ost of the nuclear magnetic resonance nages is reasonable, but several of the ltrasound images are poor by modern andards.

The book has little to offer the paediatri- an other than providing some idea of the ort of anatomical information which can e gained prenatally and on the basis of hich he or she may be approached by an bstetric colleague for discussion and dvice.

P R F DEAR

**rological Complications. Medical and urgical, Adult and Pediatric.** By FF Mar- hall. Pp 451: £62·00 hardback. Year Book ledical Publishers Inc, 1986.

urgical complications are a lucrative busi- ess these days, not only for litigation wyers but also, it seems, for medical ublishers. During the last year the subject f surgical complications has been compre- ensively covered by a number of new tles, the most recent of which is Dr larshall's book which deals with adult and aediatric urology. As two thirds of the ook is devoted to adult practice it is a elatively expensive purchase for specialists paediatric urology.

There is, however, some common round covered in the adult chapters, articularly those dealing with stone urgery, urinary diversion, and trauma. Dr eith Light's excellent contribution on the roblems of artificial sphincter surgery is nough to deter most paediatric urologists om embarking on this complex work.

Contributors to the paediatric section nclude some of the household names of merican paediatric urology; for example, r Jeffs writes on bladder exstrophy, Dr evine on hypospadias, and Dr Mitchell n urethral valves and reimplantation. outine procedures, a fertile source of omplications, have not been overlooked ith chapters on orchidopexy and cir- umcision. There is even a chapter on the omplications of antenatal intervention. his book, with its wealth of technical etail, will appeal to paediatric surgeons nd urologists.

D F M THOMAS

**My Name is Today.** By D C Morley and H Lovel. Pp 359: £2·95 paperback. Macmillan Ltd, 1986.

This book commemorates the 40th anniversary of UNICEF and pleads the cause of the most needy children in our world. Its stated purpose is to help the privileged to see and understand the problems of the underprivileged. Those concerned with children in any way must look through this book. It will make you think, smile, frown, and sometimes grimace.

The format is unusual and innovative; it is a book of ideas in pictures. There are 187 cartoons and graphs, drawn or modified by Mrs Gillian Oliver, interspersed with a dialogue between the authors, and followed by a long reading list. The theme is the health and wellbeing of the underprivileged children of the world.

Since the method is the cartoon, it is natural that there is a dependence on slogans and oversimplification of issues. One example appears in the section contrasting expenditure on armaments with that on education, homes, and health care (fig 91, p 157). 'The choice is ours'—declares the heading, but unfortunately it's not as simple as that!

There are numerous cartoons which are ideologically appealing but politically naive or not fully worked out. Some poetic licence is permissible for medicopolitical cartoonists whose purpose is to stimulate, and whose audience is not that of the academic journal. But when another objective is to inform, greater caution is needed when mixing statistical data from political and medical sources. Some figures and comments are over optimistic (fig 158 and p 299 'Many European mothers now suckle their infants for 1–3 years'), and others are difficult to believe (fig 54, p 94. Do the poor really have a lower percentage of underweight children than the economically elite? Which country?). Some figures are complicated and need more explanation (fig 60, p 102, and fig 173, p 322).

I had problems with the references and reading list. Sometimes there is a string of references in relation to a figure, and it is not clear which one is the source of the data. For example, there are nine references for fig 132. Occasionally I believe the most pertinent reference on the topic is not quoted. For example, the best reference to the 'pinch and scoop' method of measuring salt and sugar for oral rehydration (fig 140) is that of Ellerbrock (*Tropical Doctor* 1981;11:179–83). Fig 151 is about refrigerators for vaccines, but no reference is given to the three practical books on the subject from the Appropriate Health Resources and Technologies Action Group (AHRTAG).

This book is important, informative, infuriating, but challenging. The world is full of inequalities, and paediatricians concerned to minimise the effects of this unfairness on the well being of children will receive both ideas and stimulation from this book.

WILLIAM A M CUTTING

**Primary Pediatric Care.** Edited by RA Hoekelman, S Blatman, SB Friedman, NM Nelson, HM Seidel. Pp 1776: £55·00 hardback. CV Mosby Co, 1987.

This weighty North American textbook has over 200 contributors and is aimed at those who look after children in a primary care setting. The expressed aim of the book is to provide a scientific basis to primary care and to focus on 'the determinants and reflections of health and disease' rather than adopting a more traditional pathophysiological approach.

The book is divided into nine parts. Part 1 opens with an 'over view of pediatric care' and includes an account of morbidity and mortality in the young. Part 2 deals with history taking and communication skills. Part 3, on principles of patient care, concentrates on nutrition, immunisation, screening for disease, and pharmacology. Part 4, entitled 'The reproductive process' considers reproductive physiology, contraception, factors which may adversely affect the fetus, perinatal medicine, and modern obstetric techniques. Part 5 is devoted to neonatal issues including parental support. Part 6, on psychosocial problems, includes such topics as the effect of television on the family, parental abuse by children, school health, and childhood and adolescent behavioural problems. Parts 7 and 8 are the largest sections of the book and deal, respectively, with 68 common presenting signs and symptoms each considered separately (including abdominal pain, cough, haematuria, and limp) and 87 specific clinical problems (including acne, diabetes, leukaemia, phimosis, and sudden infant death). The book concludes with details of managing emergencies.

This book is a fascinating source of information for those concerned with 'ambulatory pediatrics'. The editors' intention to focus on primary care is carried through in practice—for example, having dealt with accidents as the major cause of death in childhood, there is later an extensive section on accident prevention which even includes such details as 'safety rules when meeting a strange dog'.

The book is attractively laid out, has up to date references, and is on the whole very readable, touching as it does on many aspects of general paediatric care. A minority of the content is applicable only to those practising in North America and while we may, for example, not agree that the best time for parents to see a paediatrician is before their baby is born (when circumcision is an appropriate topic for discussion), pleas to look favourably on demands for greater consumer involvement in health care are just as relevant in the United Kingdom.

I would recommend this book to general practitioners and others working in the field of primary paediatric care, but feel it will also appeal to many training for careers in hospital paediatrics.

J PUNTIS

**Physical Examination of the Musculoskeletal System.** Edited by M Post. Pp 311: £58·00 hardback. Year Book Medical Publishers Inc, 1987.

This book is written by 13 orthopaedic surgeons from North America and one from England. It describes in 12 chapters an approach to the clinical examination of the skeletal system. Two chapters are devoted to examination of children.

I cannot recommend it. I found its style turgid with a disconcerting absence of structure. The chapters devoted to children are confusing and give an impression of adult orientation. The drawings illustrating the section on neonatal hip examination, for instance, are of a much older child and the text gives the impression that the authors are not at all sure what age of child they are examining. The manoeuvres for the detection of congenital dislocation of the hip are badly described. I feel confident that if you have £58 to spend on books you could do better than this one.

D P ADDY

**Food Allergy and Intolerance.** Edited by J Brostoff and SJ Challacombe. Pp 1032: £75·00 hardback. Bailliere Tindall/WB Saunders, 1987.

The field of food allergy has been described as a model of obstruction to the advancement of learning and sadly this huge book displays the problem all too well. Sixty one chapters cover basic mechanisms, food components and their reactions, end organ effects, diagnosis, and treatment. While the sections on basic science are good, the clinical aspects tend to be dealt with in an uncritical and anecdotal way and this part of the book is very weak indeed. Paediatricians seeking sound practical guidance on food allergy will need to look elsewhere.

T J DAVID

**Clinical Endocrinology. Theory and Practice.** By Alexis Labhart. Pp 1092: DM 360 hardback. Springer Verlag, 1986.

As the title implies, this volume covers the whole field of endocrinology 'theory and practice' and as such it has much to recommend it. This is the second English edition and all but one of the authors are Swiss, many from the endocrinologically prestigious centre of Zurich. Despite the many authors the style of presentation is consistent and readable, and much of the information is provided concisely in tabular form. Subjects are considered in depth from the 'theoretical' aspect, under such headings as history, embryology, histology, biochemistry, and physiology, before embarking on the clinical practice. The chapters are well divided into specific subsections and by means of excellent indexing it is easy to locate any subject; there is some reference to almost everything. The sizeable list of references is w
selected and divided according to the s
tions.

A review for a paediatric journal m
perforce focus on its relevance
paediatricians, for whom this book has
specifically been written. Nevertheless,
authors include many eminent paedia
cians and the consideration of some
marily childhood disorders is compreh
sive; yet overall the paediatric compon
is a little lost in this large volume. Ther
not a consistent emphasis in the presen
tion of diseases of paediatric relevan
some being adequately considered, oth
with little more than a mention, a
frequently theory overrides the practi
paediatric clinical element. Those subje
which have special sections for the chi
hood disease fare better than those
which no such specific consideration
given. In diseases which are uncommon
children compared with adults, such
thyrotoxicosis or Cushing's syndrome, lit
reference is made to clinical aspects
particular importance in children, nota
growth. There is little space given to
subject of adolescent endocrinologi
problems other than reference to physi
changes of puberty included in a chapter
growth and development (in which
standard values cited, not surprisingly,
Swiss).

As this book is not written primarily
paediatric endocrinologists it is clearly
the best for them, but that was not
purpose. It serves better for adult endoc
nologists who wish to extend their kno
edge into the age range of childhood. Bu
a paediatrician is looking for a compreh
sive overview of endocrinology, and
willing to extend his interest outside t
limits of clinical childhood disease, this
certainly a worthwhile book for his coll
tion.

J M H BUCKI

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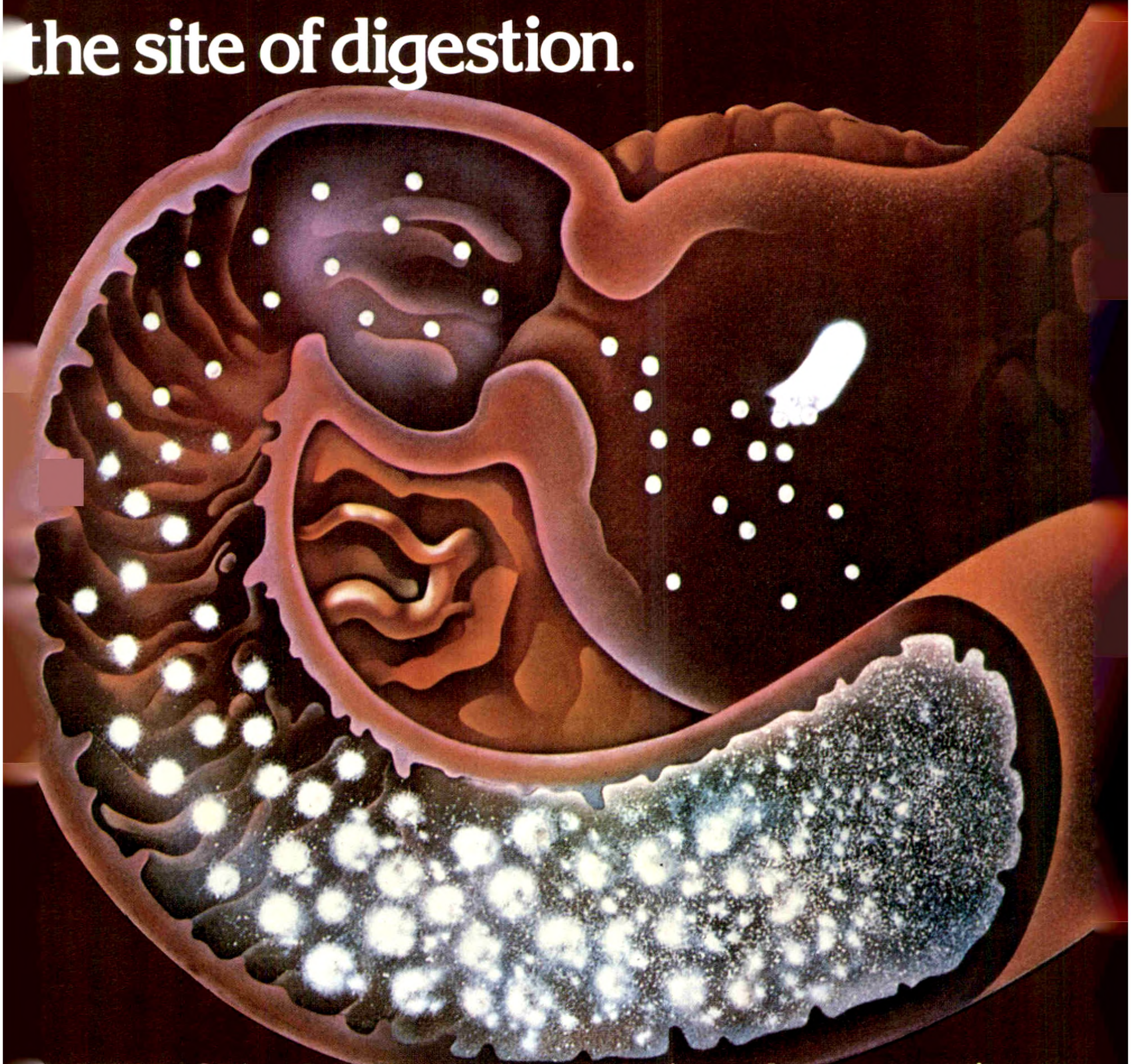

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Heft 7
Juli 1987

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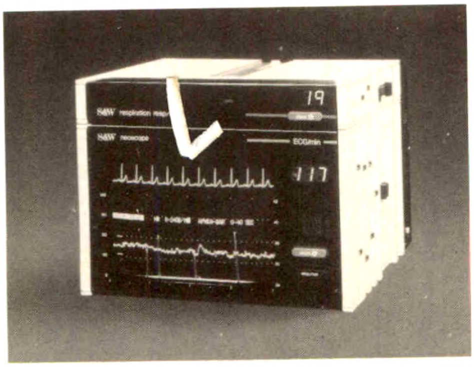

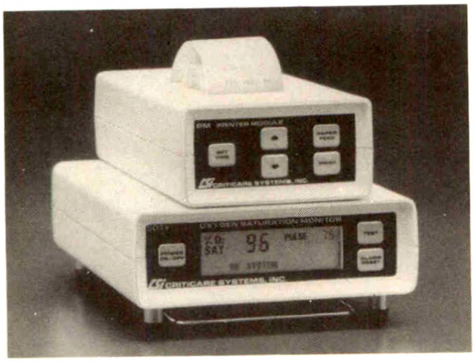

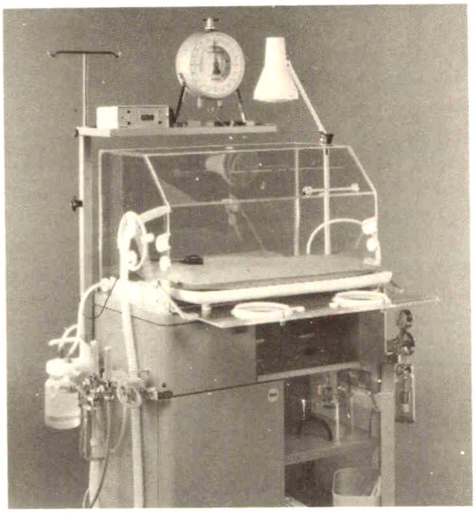

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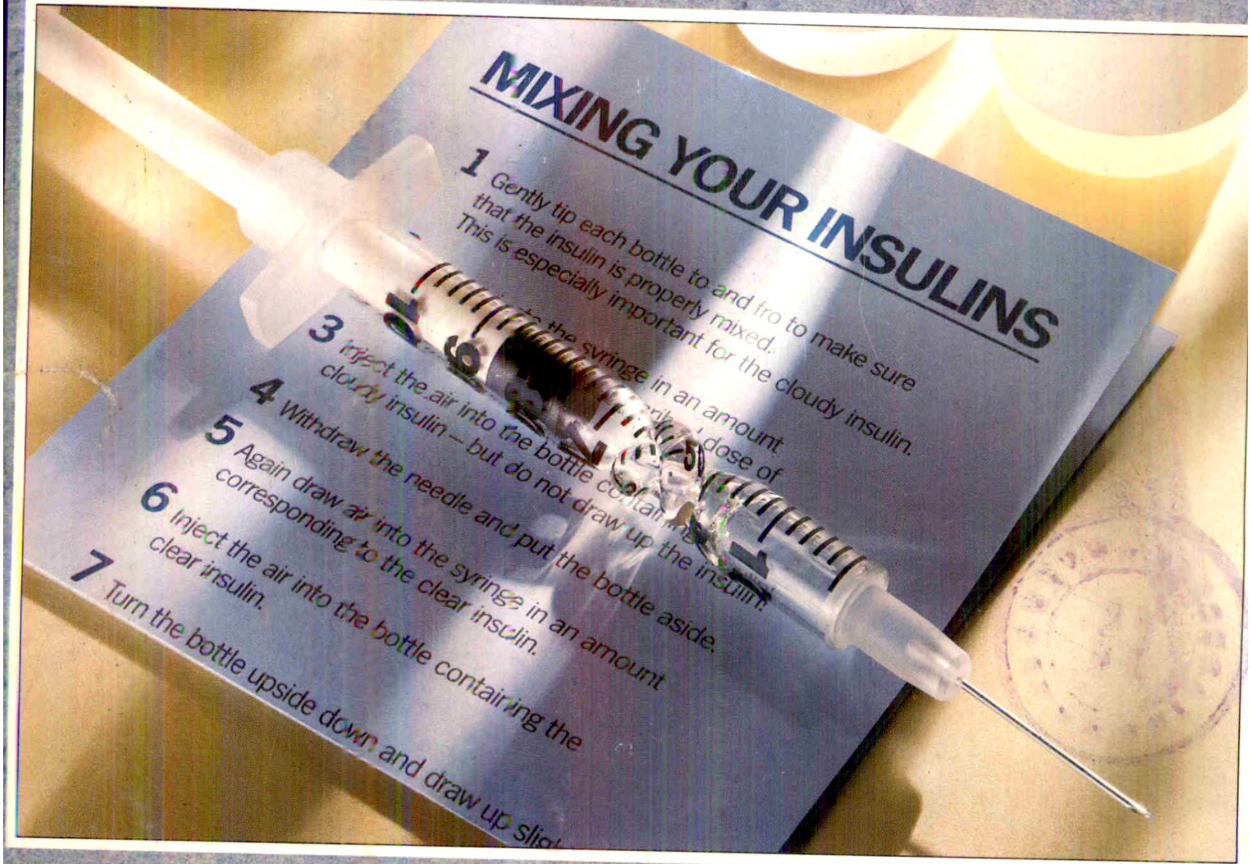

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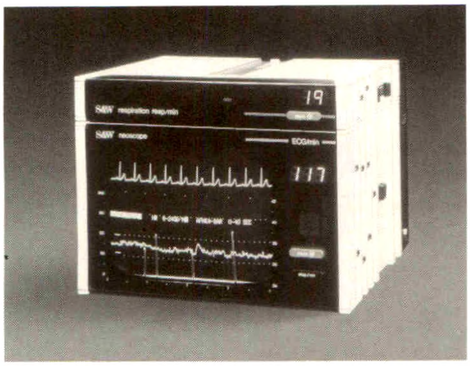

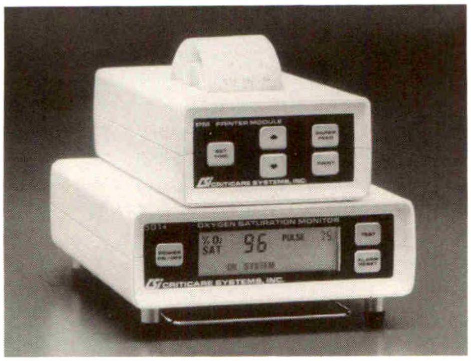

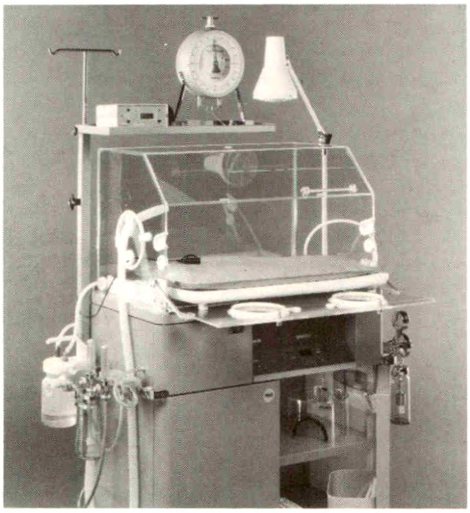

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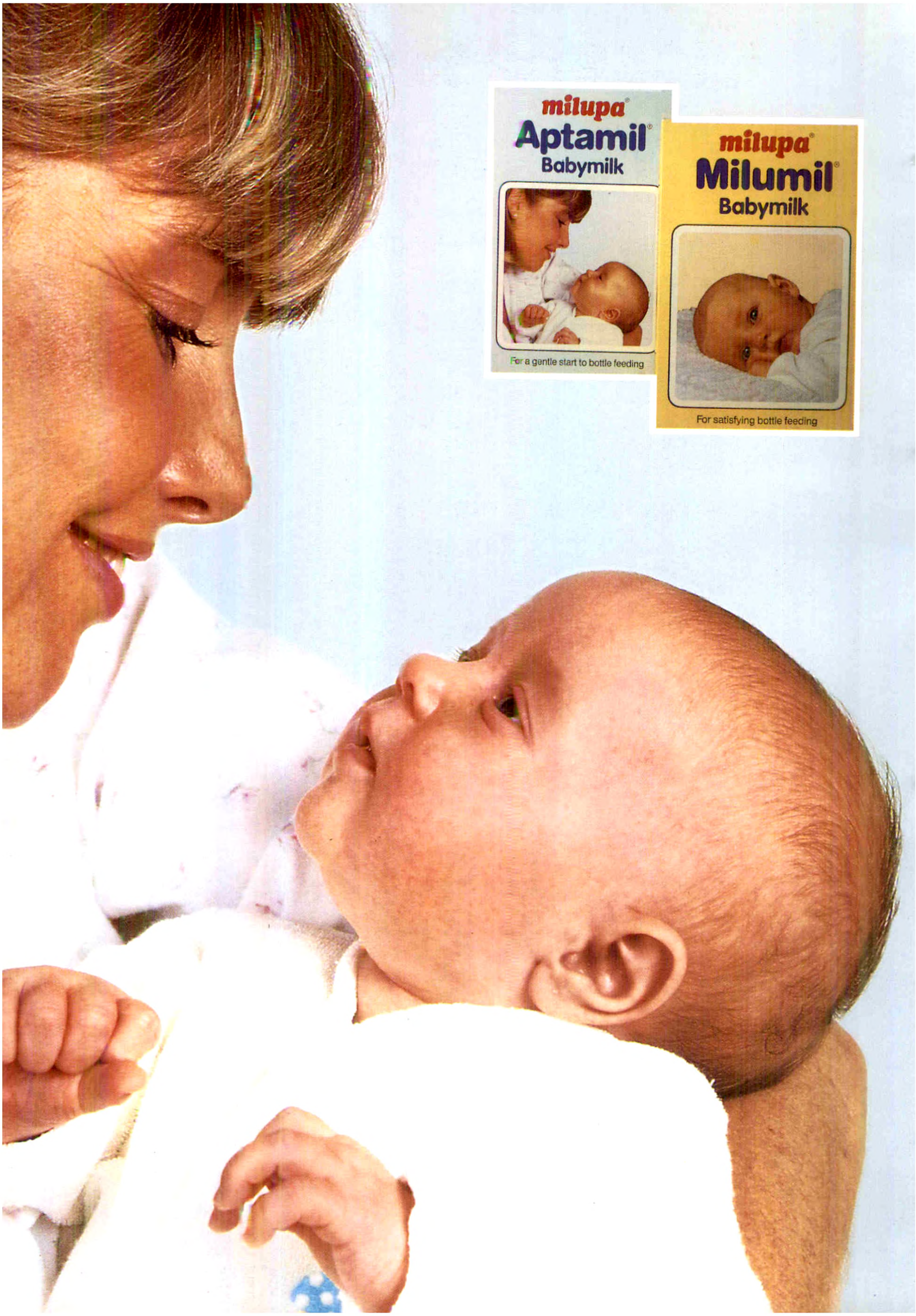
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rved. Optimum dosage is mainly determined
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toms are more helpful than
atory investigations in the early
es of hepatic failure. The onset of
ute illness, especially within the
6 months, which may include
toms of vomiting, lethargy or
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s of seizure control is an indication
nmediate withdrawal of the drug.
ence to date does not establish which
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*Archives of Disease in Childhood,* 1987, **62,** 1093

# Editorial

## The Journal Develops

In recent years papers on neonatal medicine have formed a large proportion of our publications. This reflects the increasing opportunities for investigation and treatment, and for research. In this country most paediatricians have responsibilities both for the newborn and older children and so it is essential that the Journal should cover both areas comprehensively while encouraging aspects which have a high potential for growth.

Clinicians and research workers need to know about advances in the new genetics, physiology and clinical care of the fetus and newborn, animal research, epidemiology, and neurodevelopment Important advances in research are often made when workers from different disciplines collaborate. The management and editorial committees of the 'Archives' in agreeing to develop the Journal hope to encourage this interaction

Four additional editions of the 'Archives' will be published each year dealing exclusively with papers that have a broad fetal and neonatal interest. While some papers in these areas will continue to be published in the standard edition, more technical papers will appear in the new edition. The extra editions will retain the *Archives of Disease in Childhood* title and the same format, with the papers running consecutively with a single yearly index. The additional words *Fetal and Neonatal Edition* will appear on the cover.

The decision on whether a particular paper is published in the standard or fetal and neonatal edition will be taken by the editors. Publication in the fetal and neonatal edition will not influence the prestige of that paper as it will still be cited as being published in the *Archives of Disease in Childhood.*

Both editions of the Journal for a particular month will be sent together and there will be no possibility of obtaining one edition without the other The number of pages in the standard edition will not decrease and therefore there will be more space to accept general paediatric papers of high quality.

The new editions will be managed by the present editors, associate editors, and editorial board. A small number of additional experts may be invited to join the editiorial board, depending on the type of papers submitted.

We invite authors in the fields of genetics including dysmorphism, fetal physiology and medicine, antenatal assessment including imaging techniques, the newborn including animal research relevant to clinical practice, perinatal epidemiology, and neurodevelopmental research to submit their papers for the new editions of the 'Archives' which will appear in 1988.

*Archives of Disease in Childhood,* 1987, **62,** 1094–1096

## *Annotations*

# Who needs a brain scan?

Over the last 10 years computed tomography scanning of the brain has had a remarkable effect on paediatric neurological practice. Pneumoencephalography is virtually a thing of the past, and angiography has now only a limited place. Since the review by Day and others of the use of scanning in childhood the quality, accuracy, and availability have improved greatly.

Scanning of the brain is particularly helpful in acute illnesses—for example, vascular accidents, or if there is raised intracranial pressure, or coma In the presence of progressive neurological signs it may identify or exclude the diagnosis of a space occupying lesion, hydrocephalus and some of the degenerative diseases. The indications are less certain in patients with chronic diseases, and I wish to consider four common clinical problems: epilepsy, cerebral palsy, mental retardation, and headache.

These sections can only give guidelines and are, of course, to some extent affected by the accessibility and availability of scanning, whether or not an anaesthetic is required, and the degree of anxiety felt by the family and the doctor.

### Epilepsy

There is good documented evidence that computed tomography in otherwise neurologically normal children with primary generalised epilepsy yields little useful information.[2] The yield of abnormal scans is somewhat more substantial in children with focal (partial) epilepsy and a focus on the electroencephalogram (EEG). In several series the detection of abnormalities is greater in simple partial seizures than in complex partial seizures.[3] In both these groups, however, the likelihood of finding a tumour or resectable surgical lesion is very small, especially in the pre-pubertal child.

Routine computed tomography should not be necessary in otherwise normal children with primary generalised seizures, benign rolandic epilepsy, adolescent myoclonic epilepsy, and typical absence attacks,[4] and it is unlikely that a lesion would be missed The yield of abnormalities, though they are not necessarily clear primary diagnoses, is significantly higher in children with infantile spasms (75% in cases associated with mental retardation)[5] and myoclonic astatic epilepsy (Lennox syndrome). Cerebral atrophy, periventricular calcification in tuberous sclerosis, agenesis of the corpus callosum, and cystic lesions are more common findings

There can be difficulties in interpreting the scans, and it is important that contrast enhancement should be used, otherwise certain changes can be missed Transient changes may occur possibly due to local vascular phenomena.[6] Opaque or lucent lesions may be seen which may mimic gliomas and occasionally, if the scanning is performed early in the course of a disease, a positive finding may be missed. One should be prepared to re-scan if the clinical picture warrants it This is especially true in children if the epilepsy is progressive, resistant, or appears to deteriorate or change (whatever its nature).

Computed tomography will clearly show cysts, or tumours, and macroscopic changes, but will not necessarily show small gliotic areas or cytoarchitectural changes. It may well be that in the long term magnetic resonance imaging will conclusively show these more clearly.[7]

### Mental retardation

As with generalised epilepsy, routine brain scanning in mental retardation of unknown aetiology is unlikely to give helpful diagnostic results. Lingham *et al* showed that where a scan is positive in a case of mental retardation, it is often not specific (general or focal atrophy) and would not add to diagnostic, prognostic, or genetic information.[8] Even with the many mental retardation syndromes associated with congenital anomalies, only a small percentage have a specific computed tomogram which is diagnostic

Computed tomography is more likely to lead to useful results when a primary malformation of the central nervous system is suggested by cranial size and shape. Macrocephaly may show hydrocephalus or megalencephaly. Microcephaly may show polymicrogyria or lissencephaly, and a midline malformation may show holoprosencephaly. When epilepsy is combined with retardation the positive yield is higher, as it is if epilepsy is combined with a visual deficit—for example, septo-optic dysplasia associated with optic nerve hypoplasia.

Bergstrom *et al* suggested that 20% of children with neurodevelopmental disorders had some abnormality, but most of the findings were minor—for example, some loss of substance of the brain with mild ventricular dilatation [9] These findings are difficult to interpret as we still do not know the whole range of scan findings in normal children The children who had abnormal scans were more likely to have had a seizure

## Cerebral palsy

In many cases of cerebral palsy the aetiology is not clear or unknown A scan might help to elucidate the nature of the problem and the extent, but cannot usually date the onset of the problem precisely (which might be important from the medico-legal standpoint). In many cases of symmetrical spasticity the findings on computed tomography are normal. In other cases spastic diplegia may be associated with ventricular dilatation and periventricular leucomalacia.[10] In dystonic tetraparesis an atrophic brain with ventricular dilatation may be shown. In hemiparesis there is the highest yield of abnormal findings, most commonly a cortical infarct. Occasionally in ataxic states hypoplasia or maldevelopment of the cerebellum is shown.

No sign of abnormality on computed tomography was found by Taudorf *et al* to be diagnostic of a specific type of cerebral palsy, but hemiatrophy was nearly always seen in patients with hemiplegia.[10] There was specific atrophy of the cella media in some cases with paraplegia, and it was postulated that this might represent the result of microinfarction in the periventricular area in premature children A similar suggestion was made by Barth *et al*, who found that there was a specific pattern of bilateral cortical and subcortical damage in the central regions which was compatible with birth asphyxia [11]

Thus although computed tomography may be abnormal in most cases of cerebral palsy, the findings are not usually specific enough to be helpful. Scanning is likely to be most valuable in delineating the severity of the lesion associated with hemiparesis and may give a clue to the origin of the problem in some ataxic syndromes. In some cases of diplegia, computed tomography together with other information may help date the origin of the problem

## Headache

Many parents are concerned about the possibility of a tumour as the cause of a child's headache. With isolated headache as the sole symptom in the absence of neurological findings or signs of raised intracranial pressure, important intracranial disease is unlikely to be shown by scanning. Even in adults where the likelihood of disease is higher, only 7·5% of one large series had unsuspected disease, of which one third were tumours [12] In a study of adults with classic migraine only one of 435 patients had an important abnormality,[13] and Prensky *et al* have stated that radiological investigation of children with migraine is unrewarding.[14] Transient changes have been reported in the scans of children with classic migraine which were at first mistaken for arteriovenous malformations.[15] It is likely that these changes, seen in the acute phase, represented changes in the permeability of the blood brain barrier. Adults with migraine may show a degree of atrophy when they have had migraine for a number of years, but the importance of this is not known.[16] Unless recurrent headaches have an unusual pattern, are getting progressively worse, or are associated with neurological signs, computed tomography is not really justified.

The cost of scanning, including perhaps transport to special centres and anaesthesia, is appreciable. The investigation should be performed when a diagnosis, particularly one which will affect management, is likely to be made. It must also be realised that a normal scan does not necessarily exclude an underlying pathological process. When there is no real clinical indication, as in generalised epilepsy or migraine, we should resist the pressures of parents (and doctors) to perform this examination, although occasionally I suspect many of us have given in.

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*Archives of Disease in Childhood,* 1987, **62,** 1097–1098

# Is fetal blood sampling and pH estimation helpful or harmful?

The role of continuous electronic monitoring of the fetal heart rate (EFM) in the prevention of intrapartum damage continues to be controversial [1] If all fetuses are monitored in this way, about one third will have an abnormal cardiotocogram at some stage during labour Uncritical resort to operative delivery if this happens is therefore inevitably associated with high rates of caesarean section and forceps delivery While a high rate of intervention may result in low perinatal mortality and morbidity, the mother has to shoulder the increased rate of complications, discomfort, and loss of satisfaction which often accompanies operative delivery.[2]

How then can the rate of false positive EFM be reduced? When EFM is done in conjunction with fetal blood sampling and estimation of pH there is undoubtedly a lower rate of operative delivery than when it is used alone.[1 3] There is also some evidence that high rates of fetal blood sampling reduce the proportion of neonates born with a low pH. For example, Sykes *et al* reported that in 899 births with a rate of fetal blood sampling of only 4% mean umbilical cord arterial blood pH was 7·20 [4] A similar study at St Mary's Hospital, Paddington, of 790 births with a 12% rate of fetal blood sampling reported a mean pH of 7·26.[5] Van den Berg *et al* reported 2669 births with a rate of 22% and a mean pH of 7·30 [6]

Despite this evidence of the benefits of fetal blood sampling, however, and despite the fact that in 1979 more than 90% of obstetric units in the United Kingdom used EFM, fetal blood sampling was used in only 40%.[7] The main reason for this is probably logistical, in that fetal blood sampling is time consuming and uncomfortable for both obstetrician and mother. Attempts to produce an electrode which can be attached directly to the fetus and provide a continuous measurement of pH continue, but a practical system has not yet been produced There are, however, more fundamental issues complicating the interpretation of fetal blood pH in relation to predicting neonatal outcome and the need for intervention

Impaired gaseous exchange leading to hypoxia and acidosis remains a major problem for the fetus during labour, but the fetus may also be adversely affected by infection, drugs administered to the mother, haemorrhage, and trauma (caused, for example, by breech delivery, shoulder dystocia, difficult forceps delivery, a tight nuchal cord, and prolonged head compression) In a recent study of 56 babies of more than 32 weeks' gestation at delivery who required resuscitation by intubation and ventilation only 43% had any evidence of hypoxia or acidosis shown by cardiotocographic abnormality and analysis of umbilical cord blood.[8] Even when acid base balance is disturbed, the importance of this for the fetus will depend on factors such as gestational age,[9] centile birth weight,[10] and exposure to other hazards such as meconium aspiration,[11] and trauma.[12] Thus measurement of the acid base status of the fetus alone is not a sufficient basis on which to predict outcome or decide management.

Several studies have shown that 80% of babies with a pH in fetal blood of less than 7·2 will have an Apgar score at one minute of less than 7, compared with an overall incidence of only 10–15%.[13 14] If a clinical indication for sampling is present, such as an abnormal cardiotocogram or meconium staining of the liquor, however, even babies with a fetal blood pH value of less than 7·3 still have about twice the risk of having a low Apgar score at birth than if the cardiotocogram is normal.[13] This may be related to other factors such as difficult delivery, anaesthetics given to the mother, infection, and prematurity, which are not reflected in fetal acid base balance.

Even when the pH is low, the long term implications for the fetus are uncertain. Intact survival has been reported despite an arterial pH of only 6·6 [15] This is because the likelihood of an abnormal outcome increases as pH falls but there is no definite cut off point between normal and abnormal, rather prognosis depends on many factors.[16]

There are also problems in interpreting pH measurements in the fetus. Inexperienced clinicians may easily misinterpret a reversible short term episode of fetal respiratory acidosis after an acute incident (such as maternal hypotension) as chronic metabolic acidosis unless blood gas or lactate measurements are also made.[13] On the other hand, a well grown fetus can maintain his pH for up to 90 minutes even in the presence of marked hypoxia, thus providing the clinician with false reassurance;[17] unless repeated sampling is performed, the development of serious acidosis may be missed.

These caveats do not mean that fetal blood sampling and estimation of pH are not worth while. What they should mean is that labour should be managed by staff well trained in the pathophysiology of the fetus and capable of interpreting acid base state in the context of all the other measurements available. While such interpretation is difficult and imprecise, it is no more so than the interpretation of the data available for the neonate in the intensive care baby unit. It is unrealistic to expect any single measure to provide a complete description of the condition of the fetus. Fetal blood sampling with blood gas and pH estimation must, however, remain the cornerstone of any scientific attempt to assess the health of the fetus in labour

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# Bronchopulmonary dysplasia: the outcome

Since 1980 when the last annotation on bronchopulmonary dysplasia appeared in the *Archives* there have been few advances in the understanding or prevention of this condition.[1] In spite of considerable improvements in ventilatory care it is certainly no less a problem; there is a growing population of children who are surviving improved neonatal care and who develop varying degrees of respiratory difficulty. Evidence suggests that many of these infants will require long term follow up, not only for the audit of neonatal intensive care units, but also because of their increased morbidity and mortality from respiratory problems throughout life

## Definition

Northway *et al* first described the series of changes that occurred in groups of infants with respiratory distress syndrome during prolonged ventilation.[2] This sequence included the acute and resolving stages of idiopathic respiratory distress syndrome. Now, most paediatricians would consider the criteria of Bancalari *et al* as being the most useful for follow up[3]: intermittent positive pressure ventilation during the first week of life and for at least three days; clinical signs of chronic respiratory disease for more than 28 days; supplemental oxygen for more than 28 days to maintain a $PaO_2$ of 6·7 kPa (50 mmHg); and chest *x*-ray pictures showing persistent strands of radio density and areas of increased lucency that may coalesce into large bullae.

There are many infants who do not fulfil the clinical criteria for bronchopulmonary dysplasia but who have persistently abnormal lung function. Either prematurity[4] or neonatal ventilation[5] may be the precursor of long term airway abnormalities. Thus infants fulfilling the clinical criteria may form just the tip of the iceberg as far as long term problems are concerned The problem of definition makes the assessment of incidence difficult; it has been reported as being between 2·5 and 40%[6 7] depending on the series and the range of birth weights studied

Optimal management of idiopathic respiratory distress syndrome includes careful control of ventilation and inspired oxygen,[8] treatment of patent ductus arteriosus,[9] and of intercurrent infection. Recently other therapeutic options have been suggested including high frequency ventilation,[10] the use of exogenous surfactant,[11] systemic or inhaled steroids,[12] and even inositol which may reduce the impact of bronchopulmonary dysplasia.[13]

## Outcome

The oldest survivors are still less than 20 years of age, but there are increasing numbers of studies being reported concerning the long term follow up of survivors of bronchopulmonary dysplasia. Even recent studies report a mortality of 11 to 20% after discharge,[6 14 15] and if the infant requires oxygen after 5 months of age there is a particularly poor prognosis. It may take some years before we have a complete picture of the long term outcome of the condition and a lifetime before its full impact on adult respiratory disease is known.

Follow up studies have included clinical observation, lung function tests, tests of pulmonary haemodynamics, and of bronchial hyper-reactivity. It has been shown that in the first year of life infants may have relative hypoxaemia, carbon dioxide retention, reduced lung compliance together with raised airway resistance, increased thoracic gas volume, right ventricular hypertrophy, and increased pulmonary vascular resistance. Oddly, many of these measurements may not have been abnormal before discharge from the neonatal unit[16] and they are of limited value in predicting later lower respiratory tract illness.

Subsequently these abnormalities may resolve slowly after 1 to 2 years.[17] During the first 2 years of life infants with bronchopulmonary dysplasia have an increased incidence of lower respiratory tract infections and a high risk of respiratory failure during such illnesses. It was shown in one study that more than 95% of survivors had abnormal growth, development, and *x*-ray appearances at 2 years of age,[6] while another showed a 78% incidence of abnormal *x*-ray appearances at 2 years.[18] There does not seem to be a strong correlation between radiographic resolution and symptoms among survivors.

Electrocardiographic abnormalities have also been documented. More recently cardiac catheterisation has allowed measurements of pulmonary artery pressure and pulmonary vascular resistance and their response to treatment with oxygen. In one study the degree of pulmonary hypertension did not correlate well with results of pulmonary function tests.[19] As in adults, PaO$_2$ correlated better with other measurements of pulmonary haemodynamics than routine spirometry. Continuous oxygen treatment may lead to a gradual reduction in pulmonary vascular resistance, but this requires careful supervision with frequent 24 hour tape recordings of oxygen saturation.

Spirometry has shown airways obstruction in children aged 7 to 10 years, and metacholine challenge tests were positive in 43–45%, indicating bronchial hyper-reactivity.[5 20] The increased bronchial reactivity may be a non-specific response similar to that found in children after repair of tracheoesophageal fistulas, children with cystic fibrosis, and adults with chronic suppurative lung disease. The suggestion that a genetic predisposition to hyper-reactivity may underlie the development or the progression of bronchopulmonary dysplasia is not borne out by an association with atopy

## Problems in adult life

The hypothesis that lower respiratory tract illness is a predictive factor of chronic airflow limitation in adult life has been much debated [21–23] Adults with chronic obstructive lung disease and bronchial hyper-reactivity have a more rapid deterioration in lung function.[24 25] Much of the data have been generated from retrospective studies which rely on preferential recall of symptoms in early childhood. Thus the association of chronic obstructive airways disease in relation to early respiratory problems will only be established by long term prospective studies Follow up of large numbers of survivors of bronchopulmonary dysplasia into adult life will show whether they are particularly at risk of chronic obstructive airways disease. Many other factors are likely to interact including respiratory infection, atopy, parental smoking, air pollution and socioeconomic circumstances.

## Implications

If bronchopulmonary dysplasia and clinically undetectable abnormalities of lung function are not to be precursors of long term respiratory morbidity in infants surviving prematurity and neonatal ventilation then certain preventive strategies and therapeutic regimens need to be introduced. Firstly, maintaining adequate oxygenation to reduce pulmonary hypertension is a priority. The oxygen treatment may be needed for several months or even years and even now long term home ventilation services are being established in some parts of the world.

Secondly, the prevention of further respiratory morbidity during childhood will be required. This will necessitate an increase in the use of the standard vaccinations and the use of a wider range of vaccines among preterm survivors. Prompt treatment of respiratory infections, with parents being taught physiotherapy and the provision of broad spectrum antibiotics, will also reduce further airways damage. If atopy is associated with increased bronchial hyper-reactivity this should be treated with appropriate antiasthma drugs. Hopefully intervention will reduce morbidity secondary to parental smoking, but as these infants grow into adolescence they must be advised against smoking themselves.

Finally there is a need for centres to establish a service for long term follow up of infants who survive with bronchopulmonary dysplasia to allow collection of data and help in ensuring optimum management.

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# Cyclophosphamide treatment of steroid dependent nephrotic syndrome: comparison of eight week with 12 week course

REPORT OF ARBEITSGEMEINSCHAFT FÜR PADIATRISCHE NEPHROLOGIE*
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SUMMARY In a prospective study (Cytotoxic Drug Study II), 18 children with steroid dependent nephrotic syndrome and steroid toxicity were treated with cyclophosphamide (2 mg/kg body weight/day) for 12 weeks in combination with reducing doses of prednisone (group A). This group was compared retrospectively with 18 children with steroid dependent nephrotic syndrome, studied as part of the Cytotoxic Drug Study I, and who had received cyclophosphamide for eight weeks (group B). There were no differences between the groups in age at the onset of the nephrotic syndrome, age at entry into the study, and duration of the nephrotic syndrome before entry into the study. The number of relapses during the six months before the treatment was the same in both groups. Two years after treatment 12 of 18 children treated with cyclophosphamide for 12 weeks were still in remission. By contrast, only four of 18 children treated with cyclophosphamide for eight weeks were still in remission. The cumulative rates of sustained remissions were significantly higher (67% and 22%, respectively) in group A. All relapses were observed within 400 days of stopping cytotoxic treatment. No severe side effects of cyclophosphamide occurred up to two years after treatment had been stopped. We conclude that for children with steroid dependent nephrotic syndrome and steroid toxicity cyclophosphamide treatment should be prolonged to 12 weeks to increase the likelihood of a prolonged remission.

In a previous study it was shown that 78% of children with steroid dependent nephrotic syndrome who were treated with cyclophosphamide for eight weeks relapsed soon after the treatment was stopped.[1] The question was raised therefore whether the unfavourable result in this group was due to a primary resistance to cytotoxic drugs or to the low cumulative dose of cyclophosphamide used (112 mg/kg body weight). The reported experience of other groups was controversial,[2–6] and did not answer the question because the authors did not distinguish between patients with and without steroid dependence who relapsed frequently.

The Arbeitsgemeinschaft für Padiatrische Nephrologie therefore started another prospective multicentre study in which children with steroid dependent nephrotic syndrome and steroid toxicity were treated with cyclophosphamide for 12 weeks (group A) instead of eight weeks as in the first trial (group B). This study (Cytotoxic Drug Study II) aimed to investigate the effect of a 12 week course of cyclophosphamide on the duration of remission and on the rates of relapse in children with steroid dependent nephrotic syndrome with minimal histological changes, and to compare the results of the 12 week course with those of the eight week course in the same type of patients studied in the first trial.[1]

## Patients and Methods

We studied children aged 2 to 16 years with nephrotic syndrome with minimal histological changes who responded to treatment with prednisone with complete remission, but who subsequently relapsed frequently, developing steroid dependence and becoming toxic to steroids due to the prolonged treatment with prednisone. The definitions and criteria for nephrotic syndrome, remission, and relapse were the same as those used by the International Study of Kidney Disease in Children[7] and by the Arbeitsgemeinschaft für Pädiatrische Nephrologie.[8] Patients with steroid dependent nephrotic syndrome were defined as: those in whom two consecutive relapses occurred during the alternate day prednisone treatment regimen given for an earlier relapse; or within 14 days after the end of an alternate day prednisone regimen ('fast' relapse); or in whom two of four relapses in a period of six months were fast relapses.[1] Renal biopsies were performed in each patient before starting the cytotoxic treatment. Patients previously treated with any cytotoxic drug were excluded from the study.

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*Participating centres of Cytotoxic Drug Study II: Erlangen, Universität-Kinderklinik (D Michalk), Frankfurt, Universitats-Kinderklinik (J Dippell), Hannover, Kinderklinik der Medizinischen Hochschule (J Brodehl), Heidelberg, Universitats-Kinderklinik (K Schärer), and Würzburg, Universitäts-Kinderklinik (D Gekle)

For steroid treatment only a standard initial and relapse regimen of prednisone was used.[1] The first attack was treated with 60 mg/m$^2$/day given in three divided doses (total dose not more than 80 mg per day) for four weeks, followed by prednisone on alternate days with 40 mg/m$^2$/48 hours given as a single dose on the morning of every other day for four weeks. Relapses were treated with 60 mg of prednisone/m$^2$/day until the urine had been free of protein for three days; patients were then given four weeks of treatment on alternate days at a dose of 40 mg/m$^2$

For cytotoxic treatment only cyclophosphamide at a dose of 2 mg/kg was used. In the first Cytotoxic Drug Study (CYTO I), which ran from 1977 to 1981, cyclophosphamide was given for eight weeks (total dose 112 mg/kg) Patients who were treated with chlorambucil in that study were not included in the present comparison. In the second Cytotoxic Drug Study (CYTO II), which ran from 1981 to 1986, cyclophosphamide was given for 12 weeks (total dose 168 mg/kg). The total cumulative doses remained below the accepted levels for gonadal toxicity [9, 10]

Statistical analysis was performed by Student's $t$ test, the $\chi^2$ test, and the Lee-Desu test for life table analysis[11] using the Statistical Package for the Social Sciences-X (SPSS-X) statistical software program

### PROTOCOL

Patients with steroid dependent nephrotic syndrome who fulfilled the above criteria were treated with cyclophosphamide according to the treatment protocol shown in table 1. Informed parental consent was obtained for each patient All patients were admitted to hospital for the first few days of the study The cyclophosphamide was started when the proteinuria which had indicated the last relapse had been absent for three days after standard prednisone treatment for the relapse. Reducing doses of prednisone were given (table 1) To maintain the protective effect of prednisone on leucopenia induced by cyclophosphamide, the prednisone treatment was also prolonged to 12 weeks in CYTO II. All medication thereafter was discontinued

The patients were followed up closely in the renal outpatient clinics of the participating hospitals. Proteinuria was measured daily with a strip test (Albustix) by the patient's parents. If an acute complication occurred during treatment (especially leucopenia or thrombocytopenia) cyclophosphamide was discontinued until the patient had recovered. At the end of the treatment the missed period of cyclophosphamide treatment was made up.

The effectiveness of treatment was judged by the duration of remission and the number of relapses after the full course of treatment

## Results

A total of 18 patients entered the CYTO II; seven

Table 1 *Protocols of Groups A and B*

| *Group A (1981–1986)* | *Group B (1977–1981)* |
|---|---|
| *1 Steroid responsive nephrotic syndrome with minimal histological change, steroid dependency, and steroid toxicity* | |
| *2 Relapse* | |
| *3 Prednisone (60 mg/m$^2$ of body surface area/day) until urine free from protein for three days* | |
| *Cyclophosphamide* | *Cyclophosphamide* |
| 2 mg/kg/day×12 weeks | 2 mg/kg/day×8 weeks |
| Total dose=168 mg/kg | Total dose=112 mg/kg |
| *Prednisone.* | *Prednisone* |
| 60 mg/m$^2$/48h×4 weeks | 60 mg/m$^2$/48h×4 weeks |
| 40 mg/m$^2$/48h×1 week | 40 mg/m$^2$/48h×1 week |
| 30 mg/m$^2$/48h×1 week | 30 mg/m$^2$/48h×1 week |
| 20 mg/m$^2$/48h×1 week | 20 mg/m$^2$/48h×1 week |
| 10 mg/m$^2$/48h×5 weeks | 10 mg/m$^2$/48h×1 week |
| Total dose = 1340 mg/m$^2$ | Total dose = 1200 mg/m$^2$ |

Table 2 *Details of patients studied*

| | *Group A* | *Group B* |
|---|---|---|
| No of patients | 18 | 18 |
| Male female | 7 11 | 9 9 |
| Mean (SD) age when nephrotic syndrome diagnosed | 5 8 (4·0) | 4·9 (2 7) |
| Mean (SD) age at entry to study | 8 6 (4·0) | 6 9 (2 9) |
| Mean (SD) duration of nephrotic syndrome (years) | 2 9 (2 5) | 1 9 (1·5) |
| Mean (SD) no of relapses in the past 6 months | 4·4 (1·0) | 4·8 (1 2) |
| Mean (SD) no of fast relapses | 3 3 (1·7) | 3 5 (1 8) |
| Mean (SD) cumulative dose of prednisone in the past 6 months (mg/kg/patient) | 164 7 (56) | 158 6 (84) |

girls and 11 boys were treated with cyclophosphamide for 12 weeks (group A). These were compared with 18 patients (nine boys and nine girls) who had been treated with cyclophosphamide for eight weeks in CYTO I (group B) (table 2) The age at onset of nephrotic syndrome, the age at entry into the study, and the duration of nephrotic syndrome before entry into the study were comparable in both groups.

The mean number of relapses in the six months before cyclophosphamide treatment was 4·4 in the group A and 4·8 in group B. Most of them were 'fast relapses'[1]—that is, 3·3 fast relapses patient/6 months in group A and 3·5 in group B All the patients therefore fulfilled the criteria for steroid dependent nephrotic syndrome.

The cumulative dose of prednisone administered within six months of entry into the study was the same in both groups, 158·6 and 164·7 mg/kg/patient respectively Toxic side effects of prolonged steroid treatment were seen in all patients; these included osteoporosis, cataracts severe obesity, and psychic disturbances.

All patients were followed up for at least two years. In group A 12 patients (67%) remained in complete remission without any relapse for two years, in contrast, only four patients in group B (22%) remained in remission (table 3). The difference was highly significant (p=0·018).

Using the life table analysis method of Cutler and Ederer the time sequence of relapses in both groups was analysed (fig 1).[11] The difference at two years was again significant (p=0·018, Lee-Desu test).

All relapses after cyclophosphamide treatment occurred within 400 days after the end of the treatment (fig 2). Only the patients who relapsed are shown: 14 patients treated in group B and six patients in group A. There are no differences in the time sequence of relapses.

No severe side effects of cyclophosphamide (haemorrhagic cystitis, severe infections, thrombocytopenia, or neoplastic disease) occurred during either the treatment or the following two years. The only mild and transient side effect was leucopenia (white cell count $<3\times10^9/l$). This occurred in two patients during the eighth week of the cytotoxic treatment and lead to an interruption of cyclophosphamide treatment for 11 days.

Table 3 *No of patients with or without relapse after 12 weeks (group A) or eight weeks (group B) of cyclophosphamide treatment*

| | *Group A No (%)* | *Group B No (%)* | *p* Value* |
|---|---|---|---|
| Patients with relapse | 6 (33) | 14 (78) | |
| Patients without relapse two years after treatment | 12 (67) | 4 (22) | 0 018 |
| Total patients | 18 (100) | 18 (100) | |

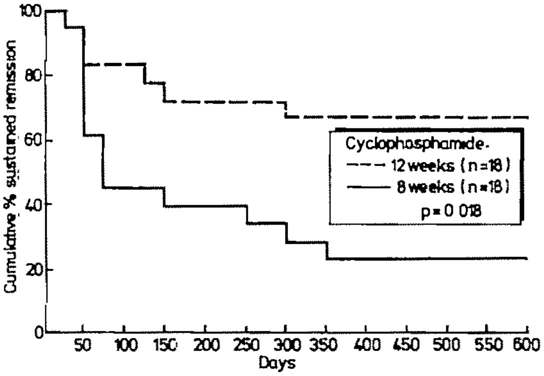

Fig 1 *Life table analysis of cumulative rate of sustained remission comparison of eight week with 12 week treatment with cyclophosphamide after two years.*

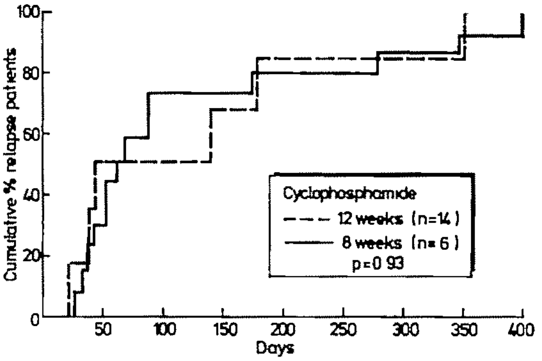

Fig 2 *Life table analysis of time sequence of relapses in groups A and B*

## Discussion

The results of the present study confirm the importance of distinguishing between two forms of frequent relapsing nephrotic syndrome, one with and the other without steroid dependency. CYTO I showed that patients who relapsed frequently but were not steroid dependent benefited from a course of cytotoxic drugs lasting eight weeks, either with cyclophosphamide or chlorambucil,[1] 72% of them remaining in prolonged remission. In contrast, those who relapsed frequently and were steroid dependent did not benefit from an eight weeks' course of cytotoxic drugs as 72% of them relapsed again soon after treatment was discontinued. A similar result was obtained by Garin *et al* in a retrospective study.[12] Some other authors have shown that higher cumulative doses of cyclophosphamide may result in longer lasting remissions.[5 13 14] Unfortunately, none of these studies reported separate evaluations of steroid dependent and non-steroid dependent patients.

Because the results of an eight week course with cyclophosphamide in steroid dependent nephrotic syndrome had already been obtained in the CYTO I study, we did not consider it ethical to repeat this part of the trial for a randomised study. We therefore studied a single group having a 12 week course of treatment, and compared the results with those of the group in the CYTO I study. This was not a strictly randomised study; the groups were, however, comparable except for the time of the study.

For group A we preferred to use cyclophosphamide alone and not chlorambucil which had been used in the previous study because there is ample evidence that the chlorambucil might produce permanent toxic damage to the male gonads in a cumulative dose over 8 mg/kg.[15 16] The cumulative dose for cyclophosphamide in this study was 168 mg/kg—that is, below 200 mg/kg, the safe borderline for gonadal toxicity.[9 10] Patients from our first cytotoxic trial were assessed five years after an eight week course of cyclophosphamide or chlorambucil and no abnormalities in gonadal endocrine function were found.[17] Feehally *et al*[18] could not detect any abnormality of cellular immune state one year after treatment of nephrotic syndrome with minimal histological changes with 2·5 mg/kg cyclophosphamide for eight weeks (cumulative dose 140 mg/kg). Nevertheless, long term side effects (such as malignant transformation) in children are still not known. Acute side effects of treatment were rare, occasionally a mild and transient leucopenia occurred which led to a short interruption in treatment. Serious side effects were not encountered.

The results of the present study give a clear answer to the question of effectiveness: in most of the children with steroid dependent nephrotic syndrome studied (67%), a prolonged remission was achieved after a 12 week course of cyclophosphamide, only 22% of those given an eight week course remained in prolonged remission.

Although the total dose of prednisone given simultaneously with cyclophosphamide was slightly higher in group A (1340 mg/m$^2$ in group A and 1200 mg/m$^2$ in group B), it is unlikely that this could be responsible for the difference. In an earlier study we showed that the amount and mode of administration of the prednisone had no lasting effect on the rate of relapse in patients who relapsed frequently.[19]

There was no difference in the time sequence of relapses between the two groups (fig 2). All relapses occurred within 400 days of stopping treatment. Although there is always a possibility of a late relapse—that is, after two years—our findings indicate that the effects of the treatment could be judged after 400 days.

We conclude that patients with the frequently relapsing nephrotic syndrome should be treated differently depending on whether their disease is steroid dependent or not steroid dependent. Using this criterion it is possible to give the lowest effective dose of the cytotoxic drug when they do become steroid toxic Patients who relapse frequently but who are not steroid dependent should be treated with cyclophosphamide (2 mg/kg/day) for eight weeks and, those who relapse frequently but are steroid dependent should be given cyclophosphamide for 12 weeks.

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## Fifty years ago

### Familial progressive diffuse cerebral sclerosis of infants

*Dorothy S Russell and K H Tallerman (London)—Arch Dis Child* 1937;**12**:71–86

Two siblings, one boy and one girl, of Jewish parents who were first cousins, died of similar illnesses The onset in the early weeks of life was heralded by reluctance or inability to suck and swallow Convulsive attacks were followed by head retraction, absence of visual recognition, rigidity, and exaggerated reflexes and extensor plantar responses Ophthalmoscopy showed no gross abnormality and no cherry red spot. Postmortem examination, obtained only in the second child, revealed gross abnormalities in the central nervous system of a degenerative nature, involving destruction in the cerebral and cerebellar cortices. Associated with this was infiltration with amoeboid forms of microglia containing lipoid material, which gave a positive reaction with Herxheimer's and Marchi's methods. Numerous astrocytes were often fibrillated with large cell bodies and clear, glassy cytoplasm. Extensive destruction of myelin was shown by ballooning of the sheaths and by wide dissemination of globular fragments of myelin Cellular infiltrations of the type seen in infections of the central nervous system were absent.

In discussing the diagnosis the authors pointed out that similar clinical features could be seen in a variety of different encephalopathies Tay-Sachs disease was excluded by the absence of the characteristic macular changes The heavy involvement of the cortex shown after death was taken to exclude Schilder's disease and Pelizaeus-Merzbacher disease. In the absence of any real knowledge of the aetiology of the different types of diffuse cerebral sclerosis in young children these two cases were considered to fall into the group earlier described by Krabbe as a familial infantile form of "diffuse brain sclerosis".

**Comment.** Krabbe's globoid body leucodystrophy is now recognised as one of the lipid storage diseases affecting the central nervous system Inherited as an autosomal recessive, deficiency of galactocerebroside β galactosidase can be shown by specific enzyme assay in leucocytes or cultured fibroblasts. Tests for heterozygotes are available

(Dorothy Russell was a distinguished neuropathologist In 194[illegible] she produced a most valuable contribution on the pathology of hydrocephalus for the special report series of the Medical Research Council I first met Kenneth Tallerman at meetings of the British Paediatric Association at Windermere before the second world war when he offered a friendly welcome to a very young Scottish paediatrician He was President of the BPA in 1958, the last year that its annual general meeting was held at Windermere )

J H HUTCHISON

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# Precocious and premature puberty associated with treatment of acute lymphoblastic leukaemia

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SUMMARY Early puberty in 28 children (23 girls, five boys) treated for acute lymphoblastic leukaemia (ALL) at a mean age of 4·0 years (range 1·4–7·8) is described. All but one had received prophylactic cranial irradiation (1800–2400 cGy) and three children had received additional cranial or craniospinal irradiation as treatment for relapse of their leukaemia. Mean age for the onset of puberty was 8·8 (SD 0·8) years in the girls and 9·3 (0·8) years in the boys; this is greater than two standard deviations from the mean for normal girls and boys. Five children (three girls, two boys) had precocious puberty. The onset of puberty occurred at greater than two standard deviations from the mean for normal girls and boys in 14(13%) girls and 4(3%) boys treated at less than eight years of age between 1970 and 1985. In a group of 55 girls treated for ALL who had survived in first remission for six years or more from diagnosis, there was a relation between young age at onset of treatment and early menarche. We suggest that premature activation of the hypothalamic-pituitary-gonadal axis occurs as a consequence of hypothalamic dysfunction due to cranial irradiation. Precocious and premature puberty in children treated for ALL may be an important factor in contributing to short stature.

The outcome for children with acute lymphoblastic leukaemia (ALL) has steadily improved since the introduction of combination chemotherapy and measures to prevent overt leukaemic infiltration of the central nervous system[1] The most common form of prophylaxis to prevent infiltration comprises fractionated cranial irradiation and a course of intrathecal methotrexate. Cranial irradiation commonly causes pituitary dysfunction when given in high doses for treatment of tumours of the central nervous system that are distant from the hypothalamic pituitary region. Growth hormone deficiency,[2] delayed puberty,[3 4] and precocious puberty[5 6] have been reported Endocrine morbidity in patients treated for acute ALL with cranial irradiation also occurs but to a lesser degree in those who have received 2400 cGy or less.[7] Partial or complete growth hormone deficiency is the commonest form of dysfunction and recently it has been recognised that its occurrence is far more widespread than previously suspected.[2 8] Nevertheless, despite the recognition of growth impairment and deviation from expected height centiles in patients with acute ALL,[8 9] most children receiving prophylaxis with cranial radiation have standing height measurements within the normal range and probably do not require growth hormone supplements.[9 10]

We have recently noticed a tendency towards early pubertal development in female survivors of ALL treated with cranial irradiation A similar finding has been reported by Pasqualini *et al* (Abstract presented at the Seventh International Congress of Endocrinology, October, 1984). We retrospectively analysed the timing and pattern of sexual maturation in children treated for ALL who presented to this hospital from 1970 to 1985.

## Patients and methods

From 1970 to 1985 inclusive, 749 patients with ALL presented to this hospital; 482 were still alive in January 1987. Pubertal maturation was assessed in all current survivors who presented during this period and who were less than eight years old at the start of treatment, who had not received testicular or whole body irradiation, and whose present age was greater than 7 years. Two hundred and thirty three children conformed to these criteria. We analysed the data of 28 of these patients (23 girls, five boys) who had evidence of early (>1·4SD) pubertal maturation. Twenty three were in first remission and five had one or more relapses All had normal serum thyroxine and thyroid stimulating hormone concentrations at the time of assessment. One girl had a family history of early puberty. Mean age at initial treatment was 3·8 years (range, 1·4–6·5) in the girls and 4·8 years (range 2·6–7 8) in the boys.

Between 1970 and 1979 patients were treated on protocols that were devised by or being piloted for the Medical Research Council Working Party on Childhood Leukaemia these have been described in detail elsewhere.[1] From 1979 onwards patients were treated by protocols devised at the Hospital for Sick Children[11] or by the Medical Research Council Working Party (UKALL X).[12] In 1972 cranial irradiation (2400 cGy in 15 fractions over three weeks) was introduced as prophylaxis against meningeal leukaemic infiltration in conjunction with a course of intrathecal methotrexate From January 1981 onwards cranial irradiation was reduced to 1800 cGy in 10 fractions over two weeks. One of the 23 patients, a girl diagnosed before 1972, did not receive cranial irradiation after induction but received craniospinal irradiation as treatment for a subsequent relapse in the central nervous system. Relapse and radiation data from the 28 patients compared with the total number of patients treated are shown in the table. Three patients, between 1970 and 1980, received 2000–2200 cGy.

Fifty five girls with ALL treated between 1971 and 1979 attained menarche. All were alive six years or more after diagnosis and had experienced no relapse of their leukaemia. The age at which menarche occurred was recorded in the case notes.

Height was measured with a stadiometer by standard anthropometric techniques[13] Puberty was staged by the method of Tanner.[14] Testicular volume was assessed with an orchidometer.[15] The attainment of stage 2 breast development in girls and a 4 ml testicular volume in boys were used to indicate the onset of puberty.[16] Normal data for the attainment of stages of sexual maturation and menarche were from Marshall and Tanner[17] [18]

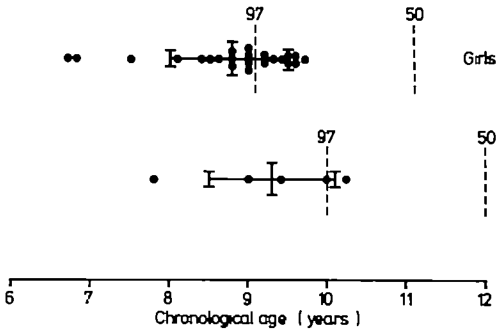

Fig 1 *Age at onset of puberty of 28 children treated for ALL at a mean age of 4·0 years (range 1·4–7·8) compared with normal values*[17] [18] *Mean age (SD) of the onset of puberty in the 23 girls and five boys is shown. These patients were taken from a total of 233 (107 girls, 126 boys) treated at less than 8 years of age between 1970 and 1985*

Table *Data of 28 children with evidence of early pubertal maturation*

| | *Sex of child* | *No with early puberty (total No assessed*)* | *Type of relapse (n=5)* | *Radiation dose (cGy)* | *Site of irradiation (No of patients)* |
|---|---|---|---|---|---|
| | | *1970–80* | | | |
| First remission | 15 girls | | | 2400 | Cranial (15) |
| | 3 boys | 18(132) | | 2000–2200 | Cranial (3) |
| Relapses | 4 girls | 4(21) | Bone marrow (4) | 2400 | Cranial (2) |
| | | | | 2400+<br>1800 | Cranial (2) |
| Total | | 22(153) | | | |
| | | *1981–85* | | | |
| First remission | 3 girls | | | 2400 | Cranial (1) |
| | 2 boys | 5(72) | | 1800 | Cranial (4) |
| Relapses | 1 girl | 1(8) | Central nervous system | 1800+<br>2400 | Cranial,<br>craniospiral (1) |
| Total | | 6(80) | | | |

*Less than 8 years old at start of treatment

Fourteen patients (11 girls, three boys) had computed tomograms taken of the brain by either a Toshiba TCT 60 scanner with hypothalamic pituitary reconstructions or an EMI scanner. Mean timing of the first scan from the onset of prophylactic central nervous system irradiation was 2·75 years (range 0·1–11·0); five patients had brain scans before one year from the onset of central nervous system irradiation. Nine patients had serial computed tomograms taken, up to a maximum of four scans.

## Results

Fig 1 shows the age of onset of puberty in the 28 patients compared with data from normal children; three girls and two boys had precocious puberty (signs of sexual maturation occurring before 8 years in girls and 9 years in boys.[19] Mean age for the onset of puberty was 8·8 (SD 0·8) years in the girls and 9·3 (0·8) years in the boys. Mean age for the onset of puberty in these 28 patients was greater than two standard deviations from the mean for normal girls[17]

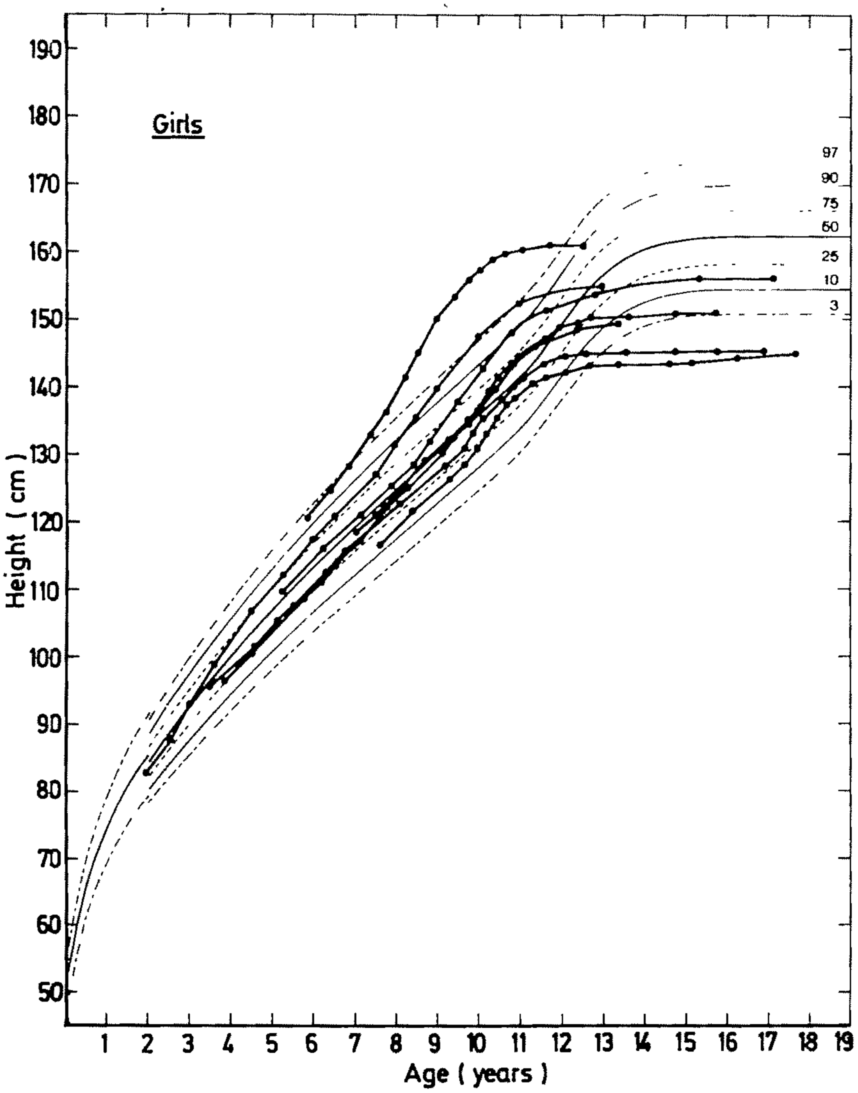

Fig 2 *Growth data from seven girls treated for ALL whose growth had been, or almost been, completed. None had received spinal irradiation Onset of the growth spurt is compared with normal values for British children*[20]

and boys.[18] The onset of puberty in patients treated during the years 1970–80 occurred at more than two standard deviations from the mean for normal girls and boys in 10 girls (14%) and three boys (4%). The onset of puberty in patients treated during the years 1981–5 occurred at more than two standard deviations from the mean for normal girls and boys in four girls (12%) and one boy (2%). In both treatment periods, 1970–80 and 1981–85, the number of girls entering puberty before two standard deviations from the mean was much greater than the 3% one would have expected in the normal population. Equivalent data for the boys were not significant. The ratio of girls to boys entering puberty at more than two standard deviations from the mean was 4:1. Unfortunately we do not have data on the timing of the onset of puberty in all patients included in this study. The onset of puberty was only accurately assessed when early sexual maturation was noticed and so our figures probably underestimate the true incidence of early puberty.

Fig 2 shows the growth of seven girls from this group where final height had been, or had almost been, achieved. The early onset of the growth acceleration can be seen when compared with the normal of Tanner *et al.*[20] Four patients had final heights equal to or less than the third centile but their growth hormone state and epiphyseal maturation had not been assessed, and no conclusion can be drawn from these data about the effect of early puberty on growth prognosis.

None of the computed tomograms showed evidence of hydrocephalus, and the ventricular size in patients who had serial scans did not change. One girl had diffuse cerebral changes that were probably due to methotrexate encephalopathy. Another girl had an empty sella; this has been associated with irradiation damage.[21]

Data relating age of onset of treatment of 55 girls with age at menarche are shown in fig 3. The younger the age at diagnosis (equivalent to age at the start of treatement) the earlier menarche occurred ($r=0{\cdot}53$, $p<0{\cdot}001$).

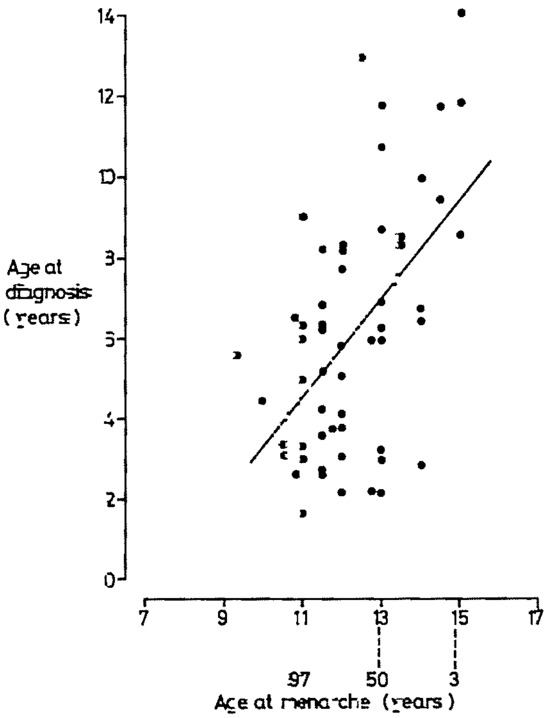

Fig 3 *Data of age at diagnosis (equivalent to age at start of treatment) and age at menarche from 55 girls with ALL, treated between 1970 and 1979 who were alive six years or more from diagnosis in first remission. All had received prophylaxis with cranial irradiation (2400 cGy, $r=0{\cdot}53$, $p<0{\cdot}001$). Normal data for menarche are shown.*[17]

## Discussion

Our data suggest that treatment of ALL is associated with the development of premature puberty, and, in a significant proportion of children, precocious puberty. Our patients retained the harmony of the sequence of acquisition of secondary sexual characteristics and the relation of these to the growth spurt that is characteristic of normal puberty.[22] Therefore, premature and precocious puberty in our patients was likely to be central (gonadotrophin dependent) in origin, although we do not have endocrinological data. The onset of pubertal development was related to the age of onset of treatment. This parallels the finding that young children are more susceptible to growth hormone insufficiency after prophylaxis with cranial irradiation in the treatment of ALL.[23]

Cranial irradiation has been reported to cause central precocious puberty in both the treatment of brain tumours in doses greater than 3300 cGy and in one girl with ALL when the dose of irradiation was only 2400 cGy[6]; this girl, however, also received intrathecal methotrexate. In our patients premature puberty was associated with doses of cranial irradiation as low as 1800 cGy. The incidence of early puberty was slightly higher in the group of patients diagnosed between 1970 and 1980. This is likely to reflect the greater proportion of children of adolescent age, but the lower dosage of 1800 cGy of cranial irradiation introduced in 1981 may also have bearing on this observation. Only greater numbers and a longer follow up will elucidate this further. Damage to the hypothalamic-pituitary axis can cause abnormal secretion of gonadotrophin releasing hormone and be associated with either precocious or delayed puberty.[3] The change in hypothalamic function that we have seen was probably caused by irradiation rather than intrathecal chemotherapy and like other endocrine effects of irradiation seems to have been delayed.[2] We found no evidence of hydrocephalus occurring as a consequence of cranial irradiation in the regimen that we used.

There was a four fold preponderance of girls with early puberty that was not accounted for by superior survival of girls over boys. In this study, when all criteria for inclusion were met, there were roughly equal numbers of boys and girls. There is a sex difference in the response to gonadotrophin releasing hormone and its analogues that may be relevant to this observation. In delayed puberty induced by pulsatile administration of gonadotrophin releasing hormone girls require lower doses than boys to maintain equivalent progress in sexual maturation.[24] By contrast, in the suppression of central precocious puberty, girls require larger doses of gonadotrophin releasing hormone analogue than boys.[25]

The growth of children with central precocious puberty is compromised by rapid epiphyseal maturation that ultimately limits growth.[19] It may well be that premature puberty, such as we have described, may cause a similar phenomenon. There are many other factors, however, such as growth hormone insufficiency, which are pertinent to the growth of children with treated ALL especially those who have been retreated after a relapse.[2] The impairment in growth caused by growth hormone insufficiency or spinal irradiation, or both, is probably masked by the early growth spurt associated with precocious or premature puberty. The net result would be a relatively normal growth velocity but with rapid advancement in epiphyseal maturation causing a reduction in adult height potential. Without regular anthropometric measurements, including sitting height and accurate assessment of epiphyseal maturation, such an effect on growth could be misinterpreted.

We believe that the recognition of premature sexual development in children with ALL may be important both for psychological and anthropometric reasons Although cyproterone acetate[26] and probably gonadotrophin releasing hormone analogues[27] do not affect the final prediction of height of children with central precocious puberty, both agents suppress sexual maturation. We agree with the suggestion of Brauner and Rappaport[6] that a combined approach with a gonadotrophin releasing hormone analogue and human growth hormone may therefore provide the best anthropometric response. Shalet has dicussed the role of endocrine deficiency and spinal growth in the impairment of the growth of children with treated ALL.[28] We wish to add to the list premature and precocious puberty as important additional sequelae.

We are grateful to Professor MA Preece, Institute of Child Health, London, for his helpful criticism of the manuscript

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# Neisseria meningitidis in a primary school

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SUMMARY A prospective study of the nasopharyngeal carriage of sulphonamide resistant *Neisseria meningitidis*, group B, type 15 P1.16, was undertaken after a cluster of four cases of meningococcal infections had occurred, two of which were fatal, during a three year period among children attending an inner London primary school. Throughout the year of the study the overall carriage and acquisition rates of meningococci were less than 6% and 1%, respectively, and were no different from those of control children of similar age and ethnic origin from another school. The outbreak strain was isolated from three children in the study school, however, but from none in the control school. A comparison of bactericidal activity in serum against the outbreak strain in children from selected classes in each school showed that there was no lack of bactericidal activity to this strain in the study school. The low prevalence of strain specific bactericidal activity in sera taken from classroom contacts of carriers, combined with the low carriage and acquisition rates, suggested a pattern of prolonged colonisation with infrequent transmission of the organism from child to child, and was consistent with the pattern of cases seen in the school.

Despite improvements in the diagnosis and treatment of meningococcal disease the mortalities of 7% for meningitis and 19% for septicaemia have not changed over the past 30 years Group B strains have consistently been the most common cause of the disease in the United Kingdom, and serotype 15, which is often sulphonamide resistant, is now superseding type 2 as the most common strain.[1] The epidemiology of meningococcal carriage has been intensively investigated in adults (originally military recruits[2]) but more recently in school and family populations.[3–6] One of these surveys showed that childhood populations of low socioeconomic group who lived in densely populated areas had an increased risk of meningococcal disease.[3]

Our study was carried out because of an unusual sequence of four cases (which occurred over three years) in a primary school. One third of the school population was of Spanish or Portuguese origin, as were three of the four cases Similarly high proportions of children of Iberian origin exist in several state schools in inner London but there was no evidence of an unusually high incidence of meningococcal infection in these or any other schools, or in the Iberian community generally. In both fatal cases the causative organism was confirmed as *N meningitidis*, group B, type 15 P1.16, which is sulphonamide resistant; in the third case the organism was isolated only from a throat swab, and in the fourth case meningococcal antigen was detected in cerebrospinal fluid by counterimmunoelectrophoresis, but cultures were sterile (table 1).

This study aimed to find out why cases of meningococcal disease were occurring regularly in this school but not in others. There were two possible patterns of spread of the organism: either it was being transmitted rapidly with a short duration of carriage (a low case:carrier ratio); or it was being transmitted slowly with a prolonged duration of carriage (a high case:carrier ratio). To investigate these possibilities we looked at rates of meningococcal carriage and acquisition as well as the prevalence of strain specific bactericidal antibody activity in children at the study school and also those in a control school with a similar ethnic population but with no reported cases of meningitis. Selected environmental studies were also carried out in the two schools

## Subjects and methods

Both schools were in the inner London area and

Table 1 *Details of four cases of meningitis*

| *Case No* | *Date of attack* | *Age (years)* | *Sex* | *Laboratory method* | *Group and type of N meningitidis* | *Outcome* |
|---|---|---|---|---|---|---|
| 1 | May 1981 | 6 | M | Countercurrent immunoelectrophoresis | Not known | Recovered |
| 2 | December 1982 | 8 | M | Throat swab | B15 P1 16 | Recovered |
| 3 | July 1983 | 11 | M | Blood culture | B15 P1 16 | Died |
| 4 | May 1984 | 3 | F | Blood culture | B15 P1 16 | Died |

they both had a similarly high proportion of children of Iberian origin. The children studied were aged 3–12 years. Swabs were taken from children after parental consent had been obtained and from those members of staff who were agreeable in May and October 1985 and February 1986. In total, 1518 swabs were taken from children during the survey, 864 from the index school and 654 from the control school. Three separate cross sectional surveys were performed, although 255 children were swabbed in all three phases and 153 children were swabbed twice. Response rates in each swabbing exercise were high. In the immediate follow up after phases one and two a smaller additional sample of swabs and blood specimens was taken from classroom contacts of carriers of the outbreak strain as well as age matched children from the control school. This was done to detect carriers who might have been missed and to determine serum type specific bactericidal activity against the outbreak strain. Blood samples were also obtained from all group B meningococcal carriers and age matched controls.

Serial dilutions of heated serum were made in sterile Hanks's solution using sterile microtitre trays and 30 dropper pipettes. A suspension of an 18 hour homologous culture from blood agar of a group B15 P1.16 strain was made in nutrient broth to about Brown's tube 2. This suspension was then further diluted to about 1/30 000 to yield a growth of 20–50 colonies a drop. Fresh guinea pig complement was diluted 1/10 and one volume of culture dilution and one volume of complement dilution were added to each serum dilution. A culture control well was also included containing one volume of culture, one volume of complement, and one volume of Hanks's solution. The tray was covered and incubated for one hour in air at 37°C. One drop from each well was then transferred to a segment of a well dried blood agar plate and incubated overnight in carbon dioxide at 37°C. The final titre is taken as 50% killing of growth in comparison with that of the control.

Swabs were taken from the posterior nasopharynx by community nurses who had received instruction on swabbing technique. The swabs were directly plated on to Thayer Martin agar containing vancomycin, colistin, and trimethoprim, and on to chocolate agar; these plates were immediately transported to the laboratory and incubated in carbon dioxide at 37°C. The plates were examined at 24 and 48 hours. All colonies which resembled *Neisseria* spp were Gram stained and tested for oxidase production. A rapid test (ONPG) for the enzyme β galactosidase was performed on all Gram negative oxidase positive cocci to exclude *Neisseria lactamica*, a common commensal of the nasopharynx in young children. Serum carbohydrate utilisation tests were then performed on all isolates negative by ONPG; those organisms utilising glucose and maltose alone were identified as *N meningitidis*. All isolates of *N meningitidis* were serogrouped and subsequently serotyped by coagglutination.

We elected to give prophylaxis to all group B meningococcal carriers while waiting for the results of typing, and arrangements were made with general practitioners to prescribe rifampicin 10 mg/kg twice daily for 48 hours. Household contacts of all group B carriers were swabbed and given prophylaxis if they were found to be carriers. Eradication of carriage was confirmed by swabbing 48 hours after completion of prophylaxis with rifampicin.

Environmental measurements in the two schools included recordings of temperature, relative humidity, and ventilation rate. Daily recordings were made in two locations (the school hall and one classroom) during July 1985.

The prevalence of meningococcal carriage in each phase was calculated as the total number of meningococci divided by the number of children swabbed. The meningococcal acquisition rate was calculated for the duration of the study as the number of newly acquired meningococci after at least one negative swab divided by the number of person months of observation.

The short duration of this survey, three swabbings at four monthly intervals, together with rifampicin, did not allow us to calculate the mean duration of meningococcal carriage.

The $\chi^2$ test with Yates's correction was used to calculate the significance of differences between the rates of carriage and acquisition and Fisher's exact test was used to calculate the significance of differences between the prevalence of type specific bactericidal activity in the two schools

## Results

The meningococcal carriage rates ranged from 3·9–2·4% in the study school and 5·6–1·8% in the control school and were not significantly different during any phase of the study ($\chi^2$=0·065; p>0·05). The 14 group B meningococcal isolates were a heterogeneous collection of serotypes and type B15 P1.16 accounted for only three of these, all from children at the study school (table 2).

In the study and control schools there were 10 and 11 newly acquired strains of *N meningitidis*, respectively, giving corresponding acquisition rates of 0·6% and 0·9% ($\chi^2$=0·89; p>0·05).

In phase one the outbreak strain was isolated from a boy in the same class (F) as the brother of the most recent child to die (case 4, table 1) The brother had received rifampicin and had been shown to be carrying the organism at the time of his sister's death 12 months previously. Because of this, repeat swabs were obtained and blood specimens were taken from 15 of the 20 children in the class, one more carrier of a group B meningococcus of a different serotype was identified.

Only four of the children swabbed in class F had detectable strain specific bactericidal activity in their serum, one of whom was the carrier who also had the highest titre. Of the carriers of other group B meningococci, three had low titres against the B15 P1.16 strain but usually had the highest titre against their homologous strain. The children tested from the control school did not have detectable bactericidal activity against the outbreak strain.

In phase two, the outbreak organism was isolated from two children in different classes who were apparently not in contact with the carrier in phase one. Children in these two classes as well as in two age matched classes in the control school had further swabs and blood samples taken. These children were aged 9 to 10 years and 10 to 11 years; 39 of 52 had blood samples taken at the study school, and 32 of 56 at the control school (table 3). The proportion of children with type specific activity in the study school classes (38%) was significantly higher than that in the control school (9%) (Fisher's exact test,

Table 2 *Meningococcal isolates from children in each phase of the study*

| | *Phase 1 (May)* | | *Phase 2 (October)* | | *Phase 3 (February)* | |
|---|---|---|---|---|---|---|
| | *Study* | *Control* | *Study* | *Control* | *Study* | *Control* |
| Total No of children in school | 299 | 215 | 275 | 212 | 290 | 227 |
| No (%) of children swabbed | 254 (85) | 167 (78) | 222 (81) | 160 (75) | 255 (88) | 184 (81) |
| No of children previously swabbed in phase 1 or 2 or both | — | — | 176 | 122 | 207 | 158 |
| Total isolates (% carriage rate) | 10 (3·9) | 3 (1·8) | 8 (3·6) | 9 (5·6) | 6 (2·4) | 7 (3·8) |
| B15 P1 16 | 1 | 0 | 2 | 0 | 0 | 0 |
| Other group B | 4 | 1 | 1* | 3 | 0 | 3 |
| Group C | 1 | 0 | 0 | 0 | 0 | 0 |
| Group Y | 0 | 1 | 1 | 0 | 0 | 0 |
| Group W135 | 0 | 0 | 0 | 0 | 0 | 1 |
| Ungroupable | 4 | 1 | 4 | 6 | 6 | 3 |

*This isolate also found in phase 1 due to failure of eradication of carriage by rifampicin

Table 3 *Sera obtained in phase 2 with bactericidal activity titre of ≥1/2 against serotype B15 P1 16*

| *Age group (years)* | *Study school* | | | *Control school* | | |
|---|---|---|---|---|---|---|
| | *No in class* | *No sampled* | *No (%) with activity* | *No in class* | *No sampled* | *No (%) with activity* |
| 9–10 | 23 | 21 | 10 (43) | 30 | 12 | 3 (23) |
| 10–11 | 29 | 20 | 5 (31) | 26 | 20 | 0 (0) |
| Total | 52 | 41 | 15* (38) | 56 | 32 | 3* (9) |

*p=0·009 (Fisher's exact test)

p=0·009). High titres of bactericidal activity were found in carriers of the outbreak strain, most of the other children with detectable activity had low titres, possibly related to cross reactions from carriage of other meningococcal strains There were no isolates of the outbreak organism in phase three and no further blood testing was done.

None of the household contacts of the group B carriers was carrying the same meningococcal strain but the parents of one child were carrying a different meningococcal serotype. In one child the rifampicin failed to eradicate the organism: the strain was not resistant and eradication was achieved with a second course.

Between 50 and 80% of the school staff were swabbed in each phase; none of them was a carrier of the outbreak strain although one teacher carried a group C non-typable meningococcus throughout the survey period.

The environmental studies showed that the temperatures in the hall of the study school were consistently higher by 3·5–4°C (the mean values for July were 19·7°C for the control school and 23·8°C for the study school). Although these measurements were only made during the one month, they showed a trend that might be continuous over the year. Ventilation studies suggested that the study school could overheat during periods of high occupancy and in hot calm weather.

## Discussion

Since 1981 there has been an increasing incidence of group B type 15 meningococcal disease in England characterised by clusters of infection in particular communities.[7] A small but worrying sequence of cases in a primary school led to this controlled study.

We did not find any significant differences in rates of meningococcal carriage or acquisition between the two schools. Both rates were lower than has been reported in other surveys which, unlike this one, were performed during epidemics.[3–6] The notable and significant difference between the two school populations, however, was that carriage of the B15 P1.16 strain persisted in children at the study school.

We established a pattern of slow transmission and prolonged duration of carriage by showing a low prevalence of the outbreak strain and a low level of type specific bactericidal activity among classroom contacts of carriers. We consistently found the highest titres of activity in the group B strain carriers rather than in the contacts, none of whom developed meningococcal disease in the time between swabbing and the administration of rifampicin. Although we do not known the length of carriage required for high concentrations of bactericidal activity to develop, these findings indicate that the emphasis should be on prophylaxis to eradicate carriage rather than on the treatment of the carriers to prevent invasive disease (as is being done in some Scandinavian countries). Recent studies using DNA fingerprinting techniques, in addition to conventional serogrouping and serotyping methods have shown that there is variation in phenotypic expression of the group and type of antigens within a strain The application of this technique to our carrier strains, particularly the non-groupable ones, might provide more useful epidemiological information.[8]

Classroom contacts of B15 P1.16 carriers with detectable bactericidal activity in serum were found in both control and study schools; the significantly higher proportion in classes of the study school can be partly attributed to the circulation of the outbreak strain as well as to the carriage of other closely related strains in these children These findings show no evidence of inability to develop immunity to the outbreak strain among the children sampled.

The environmental studies showed that in the more modern building of the study school the temperatures were higher and the ventilation systems perhaps not adequate to cope during periods of overcrowding The importance of this in the aetiology of the infections in the study school is not clear. Comparable environmental studies do not seem to have been undertaken in this country.

This study has shown that a prolonged sequence of cases of meningococcal infection may occur associated with low transmission and carriage rates and no disproportionate lack of specific immunity in the population The four cases (two fatal) that occurred in the school over three years caused considerable concern among the parents, staff, and local health authority officials. Several meetings were held between medical staff and parents to discuss appropriate treatments or investigations, or both. It had been proposed that prophylaxis with rifampicin for all the study school children and staff should be started; this suggestion was resisted, and the decision subsequently justified by the low prevalence of the outbreak strain. The unusual policy of treating all group B meningococcus carriers with rifampicin was adopted primarily because of parental concern and also because of the inevitable delay in obtaining results of serotyping. We also aimed to reduce the number of opportunities for transmission of the outbreak organism within the community. There were always some children and staff not swabbed who might have included carriers and who could therefore recirculate the organism; in addition, the swabbing procedure itself would fail to identify all carriers. These limitations were impressed on the parents before the survey was undertaken.

We felt that it was ethically unjustifiable not to give prophylaxis to the carriers of the group B strain who were identified; although no further cases have occurred, we make no claim that the extensive swabbing combined with our policy of prophylaxis has been effective in terminating the outbreak. Because of the low carriage and transmission rates in the school, however, it may be that this intervention has reduced the likelihood of further cases. Our findings should stimulate a more extensive study with more frequent swabbing to obtain more information about duration of carriage.

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# Clinical trials of penicillamine in Indian childhood cirrhosis

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SUMMARY The outcome in 15 children with advanced Indian childhood cirrhosis (ICC) treated with penicillamine 20 mg/kg/day was not significantly different from that in untreated children. Among children admitted to a further double blind trial who had ICC but who had not yet developed jaundice or ascites 10 treated with penicillamine and 10 treated with penicillamine plus prednisolone had a significantly improved survival. Fourteen of 29 treated cases made a clinical recovery and were alive 489 to 1460 days from the start of treatment. Biopsy specimens in survivors showed a return to normal liver histology in three, residual fibrosis in six, and inactive micronodular cirrhosis in five. Thus penicillamine, while not shown to be beneficial in advanced ICC, lowered mortality from 93% to 52% in pre-icteric cases of ICC.

The prognosis of Indian childhood cirrhosis (ICC) is poor.[1] Of cases presenting to the King Edward Memorial Hospital in Pune in 1979 and 1980, 45% died within four weeks, 74% within eight weeks, and 86% within six months.[2] Suggested treatment has included steroids and gammaglobulins,[3] levamisole,[4] and several traditional and 'ayurvedic' medicines. The copper chelating agent penicillamine is an obvious option for treatment because of the gross hepatic copper accumulation that is characteristic of ICC.[5 6] The poor results of chelation treatment in patients with childhood Wilson's disease who presented with advanced disease,[7] however, suggested that penicillamine could prove disappointing in ICC as most cases present at a very advanced stage. A proper trial of penicillamine was therefore indicated to forestall the introduction of an expensive, potentially toxic, and possibly ineffective treatment.

Two trials were conducted: the first included a number of advanced cases, and results were poor. This led to a second trial to which only patients who had not progressed to the development of jaundice or ascites were admitted. In this second trial a third treatment group received prednisolone in addition to penicillamine, the rationale for the steroids was their reported efficacy by other workers,[7] the inflammatory component of the hepatic pathology,[8] and the possibility that lysosomal membrane stabilisation could limit copper cytotoxicity.

## Subjects and methods

Children admitted to the King Edward Memorial Hospital in Pune in whom ICC was clinically diagnosed underwent percutaneous liver biopsy if coagulation studies permitted. If the prothrombin time was more than five seconds prolonged parenteral vitamin K and fresh donor blood were given. The Tru-Cut needle (Travenol) was used with local anaesthaesia and sedation with intravenous diazepam.

ICC was diagnosed if histological examination showed that the following features were present[9]. hepatocyte necrosis, ballooning, and hyaline inclusions; pericellular intralobular fibrosis; and granular orcein staining of hepatocytes.

### FIRST TRIAL OF PENICILLAMINE

Thirty children with histologically confirmed ICC were studied. The nature and prognosis of the disease were explained to parents and other senior family members before requesting admission to the trial. During the trial other medications such as ayurvedic drugs and liver extracts were stopped. Supportive care comprised nutritional advice and supplementation, treatment of bacterial infections, treatment with vitamin K, avoidance of non-trial medications, and conservative management of liver failure.

Fifteen packs were prepared containing 600 tablets of 50 mg penicillamine, and 15 packs containing identical placebo tablets. The packs were randomly numbered and were assigned to patients in order of admission to the trial. Children received one tablet of penicillamine or placebo per 2·5 kg/body weight/day in two doses (equivalent to 20 mg penicillamine/kg/day). Urinary protein concentration and blood count were monitored weekly for six weeks and thereafter every six weeks where possible. Compliance with treatment was encouraged by repeated home visits by paramedical health workers. In the surviving children a repeat liver biopsy was performed after six weeks if clinically possible In those children who died in hospital an immediate postmortem liver biopsy was requested Full autopsy examinations were not permitted by parents.

### SECOND TRIAL

Altogether 30 children with ICC were admitted to the trial. The criteria for admission were a histologically confirmed diagnosis of ICC and absence of ascites or jaundice. There were three treatment groups who were given penicillamine, or penicillamine plus prednisolone, or a placebo. The dose of penicillamine was 20 mg/kg/day and of prednisolone 2 mg/kg/day for four weeks and thereafter 5 mg/day Packs containing the drug(s) or placebos were randomly numbered and allocated to patients in order of presentation. In children surviving for more than three months the treatment code was broken and treatment continued with the medication the child was found to be taking.

In the interval between designing the trial and the trial packs becoming available in Pune children who would have met the admission criteria for the trial were treated with penicillamine, penicillamine and prednisolone, or vitamins (placebo) in a manner that was not blind but strictly in rotation.

In survivors of the trial penicillamine was continued until the histology of the liver was normal and hepatic copper concentrations had returned to normal.

### DATA HANDLING

Clinical and standard laboratory variables were recorded on a standard form. A semi quantitative assessment of the features of a liver biopsy specimen was made by two pathologists. Data were stored in Pune by a BBC B microcomputer with purpose written software.[10] Discs were mailed to Leicester and data transferred to the Leicester University DEC VAX computer. Comparison of baseline characteristics was performed by standard statistical methods Where the assumptions of normality and constant variance were insecure, non-parametric tests (Mann-Whitney U, Kruskal-Wallis) were used. Survival analysis was performed by program P1L of the BMDP statistical software package.[11]

### LABORATORY METHODS

The concentration of copper in the liver was assayed in sections of biopsy specimens that had been freeze dried in Pune and transferred to Leicester. A Pye-Unicam SP1 atomic absorption spectrophotometer with electrothermal atomisation was used. Standard biochemical and haematological assays were performed in Pune.

## Results

Penicillamine was well tolerated by children with ICC. Although mild proteinuria was common at presentation, this did not increase with treatment and in no child did a rash or marrow suppression necessitate stopping treatment. No complications of the liver biopsy occurred.

### FIRST TRIAL

The groups were well matched in clinical features (table 1). In both groups boys predominated and seven of 15 were jaundiced. Patients treated with penicillamine were slightly younger and two had a palpable gall bladder, which is a poor prognostic feature.[12] Results of laboratory tests showed no significant differences. Histological examination of the liver showed that no differences existed with respect to portal tract features (fibrosis, oedema, cellularity, bile duct reduplication, bile plugs, disruption of the limiting plate) or parenchymal features (fibrosis, necrotosis, hyaline inclusions, cholestasis, fat infiltration, inflammatory infiltrate, orcein staining)

Of the 30 children, only nine survived three months, and only four one year. While the median survival in treated children (58 days) was longer than in untreated (26 days) this difference was not significant. One child in each group survived to the second year then died suddenly at home: one child after measles and one after severe haematemesis. One child in each group has survived at the time of writing (more than six years). One of these, treated with penicillamine, was unusual in that his biopsy specimen at presentation showed fat infiltration in addition to the features of ICC. Follow up liver biopsy specimens showed his hepatic copper falling from 2444 µg copper/g dry weight tissue at presentation to 1935 at two months, 1569 at four months, 884 at eight months, and 36 at 20 months

### SECOND TRIAL

No significant differences existed between treatment groups for clinical, laboratory, or histological

Table 1 *Clinical and laboratory data at presentation in first trial Figures are numbers or mean (SEM*

| | *Group given penicillamine (13 boys, two girls)* | | *Group given placebo (11 boys, four girls)* | |
|---|---|---|---|---|
| No of children who had | | | | |
| Previously used steroids | 3 | | 4 | |
| Jaundice | 7 | | 7 | |
| Ascites | 5 | | 7 | |
| Dilated abdominal wall veins | 6 | | 5 | |
| Palpable gall bladder | 2 | | 0 | |
| Age (months) | 17·1 | (1·2) | 20·9 | (2·2) |
| Weight (kg) | 7·5 | (0·4) | 8·5 | (0·4) |
| Height (cm) | 72·5 | (1·2) | 75·8 | (1·8) |
| Duration of abdominal distension (weeks) | 7·1 | (1·2) | 12·9 | (3·4) |
| Liver size (cm) | 7·5 | (0·6) | 7·0 | (0·5) |
| Spleen size (cm) | 3·9 | (0·6) | 4·0 | (0·6) |
| Abdominal girth (cm) | 45·6 | (12) | 47·0 | (9·5) |
| Total bilirubin (mg/l) | 25·7 | (4·4) | 25·6 | (4·3) |
| Conjugated bilirubin (mg/l) | 10·9 | (3·0) | 9·6 | (2·1) |
| Serum glutamic pyruvic transaminase (IU/l) | 117 | (19) | 115 | (16) |
| Prothrombin time (seconds prolonged) | 6 | (1) | 7 | (3) |
| Albumin (g/l) | 37 | (3) | 40 | (1) |
| Alkaline phosphatase (IU/l) | 100 | (17) | 92 | (14) |
| Haemoglobin (g/l) | 89·0 | (5·0) | 88·0 | (5·0) |
| White cell count × 10⁹/l | 14·8 | (1·6) | 12·4 | (0·8) |
| Platelets × 10⁹/l | 203 | (8) | 251 | (47) |
| Liver copper (µg/g dry weight) | 1802 | (152) | 1808 | (219) |

Table 2 *Clinical and laboratory data at presentation in second trial Figures are numbers or mean (S*

| | *Group given penicillamine (seven boys, three girls)* | | *Group given penicillamine plus prednisolone (nine boys, one girl)* | | *Group g placebo (eight bc two girls* |
|---|---|---|---|---|---|
| No of children who had | | | | | |
| Steroids | 0 | | 1 | | 2 |
| Jaundice | 0 | | 3* | | 0 |
| Ascites* | 3 | | 1 | | 3 |
| Dilated abdominal wall veins | 2 | | 1 | | 2 |
| Palpable gall bladder | 0 | | 0 | | 0 |
| Age (months) | 18·7 | (2·2) | 15·4 | (2·4) | 21·1 ( |
| Weight (kg) | 7·8 | (0·7) | 8·1 | (0·6) | 9·2 ( |
| Height (cm) | 77 | (1) | 73 | (3) | 77 ( |
| Duration of abdominal distension (weeks) | 4·5 | (1·0) | 6·9 | (2·5) | 5·2 ( |
| Liver size (cm) | 56·5 | (5·6) | 62·5 | (5·8) | 66·5 ( |
| Spleen size (cm) | 29·5 | (7·4) | 33·5 | (7·2) | 29·5 ( |
| Abdominal girth (cm) | 44·3 | (2·0) | 41·9 | (17) | 44·1 ( |
| Total bilirubin (mg/l) | 11·4 | (1·8) | 14·5 | (4·7) | 20·4 ( |
| Conjugated bilirubin (mg/l) | 7·4 | (0·7) | 8·3 | (3·5) | 8·4 ( |
| Serum glutamic pyruvic transaminase (IU/l) | 91 | (9) | 77 | (15) | 110 ( |
| Prothrombin time (seconds prolonged) | 4·5 | (1·0) | 4·4 | (1·6) | 5·5 ( |
| Albumin (g/l) | 36 | (2·1) | 35 | (5·8) | 34 ( |
| Haemoglobin (g/l) | 100·0 | (8·0) | 101·0 | (9·0) | 97·0 ( |
| White cell count × 10⁹/l | 11·8 | (2·1) | 11·3 | (1·3) | 11·5 ( |
| Platelets × 10⁻⁹/l | 157 | (28) | 207 | (28) | 168 ( |
| Liver copper (µg/g dry wt) | 972 | (263) | 1707 | (96) | 1044 ( |

*Jaundice or ascites were absent at presentation but became apparent before treatment was started variables (table 2). Despite the earlier stage of their disease compared with children in the first trial, nine of 10 untreated children died within 181 days, median 58 days. One untreated child recovered spontaneously and was alive at the time of writing (2·7 years).

At the time of writing five children treated with penicillamine and five treated with penicillamine plus prednisolone survive 489–1460 days from the start of treatment. Life table analysis showed a significantly improved survival in both treatment groups compared with the group taking the placebo ($p<0·05$). No difference in survival existed between the two treatment groups. When these two groups were pooled the difference in survival between treated children (n=20) and the group taking placebo (n=10) was highly significant ($p<0·005$) (table 3).

Thirteen children who were eligible for admission to the second trial but who presented before the treatment packs were available were allocated to treatment groups in rotation. Inclusion of these children (five treated with penicillamine, four treated with penicillamine and prednisolone, and four given only supportive treatment and vitamins) did not introduce any differences between groups at entry but further increased the significance of the difference between survival in treated and untreated children (table 3).

Table 3 *Comparison of survival distribution in treated and untreated ICC*

| *Groups* | | *p Value* |
|---|---|---|
| **First trial:** | | |
| Penicillamine (n=15) | *v* Placebo (n=15) | 0·33 |
| **Second trial (double blind):** | | |
| Penicillamine (n=10) | *v* Placebo (n=10) | 0·01 |
| Penicillamine/ prednisolone (n=10) | *v* Placebo (n=10) | 0·04 |
| Penicillamine (n=10) | *v* Penicillamine/ prednisolone (n=10) | 0·85 |
| Penicillamine and penicillamine/ prednisolone (n=20) | *v*. Placebo (n=10) | 0·004 |
| **Combined results of preicteric 'blind' and 'non-blind' cases:** | | |
| Penicillamine (n=15) | *v* Placebo (n=14) | 0·002 |
| Penicillamine/ prednisolone (n=14) | *v* Placebo (n=14) | 0·002 |
| Penicillamine (n=15) | *v* Penicillamine/ prednisolone (n=14) | 0·97 |
| Penicillamine with or without prednisolone (n=29) | *v* Placebo (n=14) | <0·00005 |

Life table analysis was performed using program P1L of the BMDP package,[11] and the equality of survival between groups tested by the Mantel-Cox statistic

Taking all the 29 children treated with penicillamine or penicillamine and prednisolone, a comparison was made between the 14 who survived and the 15 who died to determine whether there were features at entry to the trial that could have predicted a better outcome. Five of 15 non-survivors developed jaundice between presentation and the start of treatment. Non-survivors had larger spleens, higher serum bilirubin concentrations, longer prothrombin times, and higher hepatic copper concentrations, although these differences did not achieve significance (table 4)

There were 33 liver biopsies performed at follow up in the 14 surviving children. Because of the distance of their homes from Pune and the reluctance of their parents to allow further stays in hospital after clinical improvement biopsies were performed irregularly but all children had one follow up examination and six had three. While five of 14 biopsy specimens taken within six months of starting treatment still showed features of ICC a transition was seen in successive biopsy specimens through the following stages (i) cirrhosis with thick septae and continued inflammatory infiltration, (ii) inactive micronodular cirrhosis with thin septae, no inflammation, and healthy parenchyma; (iii) incomplete fibrous septae partially dividing a healthy parenchyma, and (iv) almost normal appearances with mild portal fibrosis. At the latest follow up three children had almost normal biopsy specimens, six had incomplete fibrous septae, and five had inactive micronodular cirrhosis.

The concentration of copper in the liver fell at varying rates in different children and was <100 μg/g dry weight in only five of the 12 biopsy specimens taken seven to 36 months after starting treatment (table 5).

## Discussion

Before conducting the first trial careful consideration was given to the need for a placebo group. Because of continuing controversy as to the definition and prognosis of ICC[1] published data would not form an accurate comparison with the treated group. Cases of ICC previously treated in Pune were also not acceptable because the trial protocol included a standard of supportive care that was provided without charge to the family, and which had not previously been available.[2] For the second trial,

Table 4 *Comparison of clinical and laboratory features between survivors and non-survivors in preicteric children with ICC treated with penicillamine and penicillamine/prednisolone Figures are numbers or mean (SEM)*

| | *Non-survivors (13 boys two girls)* | *Survivors (12 boys, two girls)* | *p Value* |
|---|---|---|---|
| No of children who had | | | |
| Steroids | 1 | 2 | |
| Jaundice | 5* | 0 | |
| Ascites* | 3 | 2 | |
| Veins | 1 | 2 | |
| Gall bladder | 0 | 0 | |
| Age (months) | 18·3 (1·7) | 17·8 (2·4) | 0·87 |
| Weight (kg) | 7·9 (0·4) | 8·3 (0·5) | 0·61 |
| Height (cm) | 75·5 (1·6) | 74·9 (2·4) | 0·85 |
| Duration of abdominal distension (weeks) | 5·4 (1·2) | 8·6 (3·7) | 0·43 |
| Liver size (cm) | 6·5 (0·4) | 5·5 (0·5) | 0·15 |
| Spleen size (cm) | 5·4 (1·5) | 2·5 (0·6) | 0·09 |
| Abdominal girth (cm) | 43·2 (1·2) | 43·5 (1·5) | 0·89 |
| Total bilirubin (mg/l) | 17·5 (3·2) | 10·3 (1·7) | 0·06 |
| Conjugated bilirubin (mg/l) (n=12) | 8·2 (1·7) | 4·3 (1·4) | 0·10 |
| Serum glutamic pyruvic transaminase (IU/l) | 100 (11) | 82 (11) | 0·28 |
| Prothrombin time (seconds prolonged) | 6·2 (1·6) | 3·9 (0·6) | 0·19 |
| Albumin (g/l) | 37·2 (1·3) | 35·4 (1·8) | 0·45 |
| Alkaline phosphatase (IU/l) | | | |
| Haemoglobin (g/l) | 97·0 (6·1) | 103·0 (8·0) | 0·58 |
| White cell count $\times 10^9$/l | 9·4 (0·7) | 12·8 (1·8) | 0·10 |
| Platelets $\times 10^9$/l | 189 (15) | 145 (51) | 0·47 |
| Liver copper (µg/g dry weight) | 1549 (152) | 1258 (173) | 0·20 |

*Jaundice or ascites were absent at presentation but became apparent before treatment was started

Table 5 *Histological findings and concentration of copper in the liver in follow up biopsy specimens of children with ICC treated with penicillamine and penicillamine/prednisolone*

| | *Months from presentation* | | | | |
|---|---|---|---|---|---|
| | *0–6* | *7–12* | *13–24* | *25–36* | *>36* |
| Indian childhood cirrhosis | 5 | | | | |
| Cirrhosis with thick septae and inflammation | 3 | 1 | | | |
| Micronodular cirrhosis with thin septae | 5 | 2 | 3 | 3 | 1 |
| Incomplete fibrous septae with normal parenchyma | 1 | 2 | 1 | | 2 |
| Mild portal fibrosis | | | 1 | 2 | 1 |
| Liver copper µg/g dry weight | | | | | |
| No | 11 | 4 | 4 | 4 | 2 |
| Mean | 977 | 385 | 82 | 143 | 365 |
| Range | 68–1973 | 28–895 | 10–161 | 33–323 | 325, 40 |

in which the cases were by definition at a less advanced stage of the disease, data as to prognosis without treatment did not exist, and so a placebo group was again necessary. As a difference between treated and untreated cases appeared, termination of the trial was considered. Interim results were presented for discussion at two scientific meetings and continuation of the trial to achieve significance was urged by those taking part.[13] The significantly improved survival in patients treated with penicillamine seen in the second trial now makes it unacceptable for any future trial of penicillamine to include a placebo group.

The untreated children in this study show the grim prognosis and fulminant course of ICC. Even those children who did not have ascites or jaundice at presentation declined rapidly, 13 of 14 dying within 165 days. Before the first trial the mortality of ICC without treatment was estimated to be about 90%, and a power calculation shows that the chance of detecting a true halving of this mortality would be 90% at the 5% significance level if 15 children were included in both groups. The fact that there was no difference in survival between the two groups in the first trial has two possible explanations. Firstly, penicillamine may be genuinely ineffective in advanced ICC. The extensive hepatocellular damage seen in this condition, the clinical condition of the affected children, and the failure of penicillamine to improve survival in Wilson's disease presenting with fulminant hepatic failure all support that conclusion. Secondly, penicillamine may have a therapeutic effect that would only become apparent in a larger trial. Because of the disappointing results in the first trial, subsequent cases presenting with advanced ICC have not been treated with penicillamine. With the results of the second trial now available treatment in advanced ICC must be reconsidered.

In the second trial penicillamine alone and in combination with prednisolone improved survival. As there were no differences between results in the two treatment groups it is legitimate to make a comparison between all treated children, where 14 of 29 survived, with the sole survivor of 14 untreated children. Two further treated children made a clinical recovery but died in the second year (at 440 and 448 days of treatment) from the effects of portal hypertension and cirrhosis. Treated children had few side effects of penicillamine. Compliance, as judged by the number of tablets remaining when the family members were visited, was good.

Although absence of jaundice or ascites were criteria for admission to the second trial, jaundice did become apparent in six children in the interval between admission to hospital and the start of treatment. Five of these were in active treatment groups (one taking penicillamine, four penicillamine plus prednisolone), and none survived (table 4) This further emphasises the rapid course of ICC and the need to start chelation treatment promptly.

The rationale for penicillamine use was removal of copper from the liver by chelation, and treated patients indeed showed a progressive fall in hepatic copper concentration. This carries the implication that more effective decoppering agents such as ammonium thiomolybdate may have a role in advanced disease.[14] [15] Other modes of action are, however, possible. Firstly, penicillamine as a sulphydryl donor may regenerate reduced glutathione so protecting against cytotoxic injury If this is so then other agents with similar actions such as acetyl cysteine may have an acute therapeutic role Secondly, penicillamine may interfere with collagen synthesis by preventing cross linking of collagen chains. ICC is characterised by aggressive pericellular intralobular fibrosis and serum markers of collagen biosynthesis are present in high concentrations.[16] Although it seems unlikely that an effect on collagen could achieve so rapid a difference in survival between treated and untreated groups, it may contribute to the reduction in fibrosis seen in treated patients in subsequent biopsy specimens. Thirdly, penicillamine may reduce the concentration of circulating immune complexes Unpublished results (Vergani *et al*) show increased concentrations of serum immune complexes in ICC, their concentration increasing with disease severity. Their presence in other liver disorders, however, suggests that they are a result rather than a cause of liver cell injury Fourthly, there is increasing interest by rheumatologists in penicillamine as an anti-inflammatory drug, its action mediated by the superoxide dismutase like action of the copper-penicillamine chelate.[17] [18] The lack of side effects of penicillamine in ICC is similar to Wilson's disease but contrasts with rheumatoid arthritis.[18]

In the presence of penicillamine, prednisolone has not been shown to confer additional benefit. Conversely, it was not associated with adverse effects, and with the completion of the trial it was decided to continue treatment of preicteric cases with penicillamine either with or without prednisolone in alternate allocation to see whether there is a difference from larger patient groups. As the number of children treated with penicillamine increases it will become possible to define more accurately favourable and unfavourable prognostic features (table 4) by discriminant analysis.

The clinical recovery from ICC was associated with progressive improvement in histology. These results (to be presented in more detail elsewhere) showed a progressive evolution from ICC to: (i) active cirrhosis with thick inflammatory septae, (ii) inactive micronodular cirrhosis; and (iii) an apparently normal parenchyma with thin fibrous septae. There are few other diseases in which established cirrhosis has been shown to be reversible. The evolution of ICC to inactive micronodular cirrhosis raises the possibility that some children with cryptogenic cirrhosis who are older than those with ICC at presentation may have had a similar aetiology The occurrence of ICC and inactive micronodular cirrhosis in siblings and a history of copper ingestion in infancy in some cases of inactive micronodular cirrhosis support this conclusion.[19]

While ICC may be totally preventable by change in feeding practices in infancy,[20] [21] the present results indicate that treatment of preicteric patients with penicillamine improves survival from 10% to

45% and provides a basis for further improvements in treatment

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# Teenagers and their health

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SUMMARY Six hundred and forty three children aged 14 to 16, attending three upper schools in Oxfordshire, filled in a health questionnaire. Although over 90% rated their health as fair or good, three quarters had taken medicine in the previous four weeks, three quarters had complained of headaches, and three quarters had had dental fillings. In addition, a third drank alcohol at least once a week, a third felt depressed at least once a week, and a third had had time off school for illness in the previous four weeks. There were strong associations between smoking tobacco and other forms of drug abuse.

On the positive side, most children felt responsible for their own health with three quarters agreeing that good health is mainly due to sensible living. Over 85% turned first to their parents for medical advice.

Fashions and attitudes to health and medical problems among teenagers fluctuate over short periods of time in much the same way as do their other behaviour patterns, such as manner of dress, musical tastes, emulation of popular heroes and so on. In addition the degree to which they are exposed to certain kinds of decisions and pressures concerning the use of drugs, the expectation of earlier sexual relationships, and the prospect of unemployment on leaving school, for example, have greatly increased. Parents, doctors, and teachers may therefore find it difficult to give clear advice when consulted by this age group because of lack of knowledge and not having come to terms with such morally challenging problems themselves

These changes combined with the perception that teenagers have few medical problems could explain the lack of reliable information concerning their health needs, interests, and attitudes.[1] [2] Detailed and up to date information must surely, therefore, be vital to all those concerned with health promotion and the health of school children including the children themselves, their parents, doctors, nurses, teachers, and health educators.

The present study was undertaken to obtain the views of this age group about their health and health problems, to provide a suitable database that could be updated at regular intervals.

## Methods

The study was undertaken in the spring and summer of 1985 at three of the 36 'upper' coeducational comprehensive schools in Oxfordshire. They were selected to be representative of the whole fourth year 'upper school' population of the district. Two schools were therefore urban, one more middle class than the other, and the third covered a small town and rural population. The subjects were all children aged 14 to 16.

No detailed information concerning social class was available from the schools and the teachers felt that it would be inappropriate to ask about parents' occupations in the questionnaire. After obtaining parental permission the children were, in cooperation with the teachers, given a general health questionnaire containing 40 questions most of which were multiple choice; a few more were open ended Although the questionnaire was designed by the authors, several of the questions had been used in previous studies.[2] [3] The questionnaire was anonymous, self administered, and given to all the pupils in each school in their classrooms at the same time. It was given to the pupils by the researchers, and was preceded by a short explanation of the purpose of the study, at the end the researchers collected the questionnaires without them being seen by the teachers.

## Results

Of the total of 770 children, 643 (83%) fully completed the questionnaire. The parents of 48 (6%) of the children refused to let them fill it in; 72 (9%)

were absent the day the questionnaires where given, and 17 questionnaires were spoilt or incomplete (2·5% of those given out). Of the 643 children completing the questionnaire, 299 were girls, of whom 102 were aged 14, 196 were 15, and one was 16. Of the 344 boys, 125 were aged 14, 217 were 15, and two were 16

GENERAL HEALTH

Analysis of the questionnaire showed that whereas 45% felt they had some health problem at the time the questionnaire was filled in, only 1% felt that their health was 'poor', 7% felt their health was 'excellent', and 92% felt it was 'fair' or 'good'. Table 1 lists the more commonly mentioned health problems (asked by an open ended question).

VISITS TO THE GENERAL PRACTITIONER

Thirty seven per cent had seen their general practitioners in the previous three months, girls more so than boys—42% compared with 33% ($\chi^2=4{\cdot}41$, $p<0{\cdot}05$). Table 2 lists the most common reasons (asked by an open ended question).

TIME OFF SCHOOL

Thirty seven per cent had had time off school in the previous four weeks; of these, 53% had been off for one or two days, 40% for three to seven days, and 7% for seven days or longer. Forty two per cent of girls had been off compared with 33% of boys ($\chi^2=5{\cdot}32$, $p<0{\cdot}02$). Table 3 shows the reasons given for taking time off school (asked by an open ended question).

MEDICINES

Seventy per cent had taken medicines in the previous four weeks but this was significantly more common among girls 77% compared with 63% ($\chi^2=13{\cdot}99$, $p<0{\cdot}001$). Nineteen per cent of all the children were taking medicines at the time the questionnaire was filled in. Table 4 gives the reasons for taking medicines in the previous four weeks (asked by an open ended question). The main

Table 1 *Children's health complaints at time of questionnaire*

| *Complaints* | *No of children (%)* |
|---|---|
| Coughs and colds | 84 (13) |
| Hay fever | 34 (5) |
| Skin problems | 31 (5) |
| Asthma/bronchitis | 24 (4) |
| Headache | 16 (2) |
| Throat infections | 10 (2) |
| Joint problems | 16 (2) |
| Weight problems | 14 (2) |
| Eye problems | 12 (2) |
| Injuries | 9 (1) |
| Smoking | 9 (1) |
| Stomach problems | 9 (1) |
| Other | 64 (10) |

A few children mentioned more than one problem

Table 2 *Reasons for children's visits to their general practitioners during previous three months*

| *Complaints* | *No of children (%)* |
|---|---|
| Sore throat | 43 (7) |
| All injuries | 28 (4) |
| Gastrointestinal problems | 26 (4) |
| Skin problems | 26 (4) |
| Immunisations | 17 (3) |
| Eye infections | 13 (2) |
| Coughs and colds | 13 (2) |
| Stomach aches | 13 (2) |
| Infectious diseases | 11 (2) |
| Headache | 10 (2) |
| Chest infections | 9 (1) |
| Hay fever | 8 (1) |
| Influenza | 6 (1) |
| Asthma | 4 (1) |
| Period pains | 12 (4) |
| Contraceptive pill | 6 (2) |
| Other | 61 (9) |

A few children gave more than one reason for visiting the doctor

Table 3 *Reasons that children gave for taking time off school during previous four weeks*

| *Reason* | *No of children (%)* |
|---|---|
| Gastrointestinal problems | 55 (9) |
| Coughs and colds | 42 (7) |
| Influenza | 24 (4) |
| Headaches | 21 (3) |
| Sore throats | 19 (3) |
| Injuries | 9 (1) |
| Infectious diseases | 6 (1) |
| Ear problems | 4 (1) |
| Period pains | 4 (1) |
| Others | 31 (5) |

Table 4 *Children taking medicines for various health problems during previous four weeks*

| *Problem* | *No of children (%)* |
|---|---|
| Headaches | 257 (40) |
| Coughs and colds | 55 (9) |
| Stomach aches | 26 (4) |
| Hay fever | 23 (4) |
| Asthma | 9 (1) |
| Influenza | 8 (1) |
| Ear infections | 8 (1) |
| Acne | 5 (1) |
| Period pains | 33 (11) |
| Others | 42 (7) |

medical reason was self treatment for headaches with such products as paracetamol and aspirin. Medication taken at the time of the questionnaire were mainly for hay fever (reflecting the time of year), coughs and colds, and headaches, all in roughly equal numbers

### SKIN PROBLEMS

Twenty three per cent had skin problems and again their was an obvious sex difference with 31% of girls noting them compared with 17% of boys ($\chi^2=17{\cdot}4$, $p<0{\cdot}0001$); the commonest problem was, not surprisingly, acne. Just over half of all the children had had warts or verrucas, or both, at some time.

### HEADACHES

These occurred in 84%, with 20% suffering from them at least once a week, 33% once a month, and 31% less frequently. Significantly more girls than boys suffered from headaches ($\chi^2=15{\cdot}5$, $p<0{\cdot}001$). Of those suffering from headaches, however, only 3% gave them as a reason for taking time off school and 2% as a reason for visiting their general practitioner Sixty nine per cent of the children with headaches took aspirin for relief.

### ACCIDENTS

Although there was no significant difference between the numbers of boys and girls among the 24% of children who had had an accident in the previous month, there were sex differences in the type of accident. Thus 36% of the accidents were sports injuries and these were more likely to occur in boys than girls ($\chi^2=4{\cdot}22$, $p<0{\cdot}05$) as were the 12% of cycling accidents ($\chi^2=4{\cdot}63$, $p<0{\cdot}05$).

### DEPRESSION

Eight per cent of all children felt fed up or depressed every day, and 28% at least once a week Only 3% of girls and 7% of boys had never felt depressed.

### ASTHMA/HAY FEVER

Eleven per cent of all the children considered that they suffered from asthma, and 68% of these thought that it interfered with their work or sport. An additional 34% also said that they suffered from hay fever or other allergies, and half of them thought that it interfered with their work or sport

### SMOKING, ALCOHOL, AND DRUGS

Almost all (98%) of the children thought that smoking harmed 'your health' and 85% thought that smoking harmed other people's health (passive smoking); only 7% agreed with the statement that 'there is nothing wrong with smoking'. Even at this age, however, 21% were smoking at the time the questionnaire was given (24% of the boys, and 18% of the girls, ($\chi^2=3{\cdot}29$, $p<0{\cdot}05$)). Most smoked between two and 10 cigarettes a day, and 56% of all the children's parents smoked. There seemed to be a significant correlation between smoking and other forms of drug abuse. Thus smokers drank alcohol considerably more often; 52% were drinking at least once a week compared with 24% of non-smokers ($\chi^2=36{\cdot}56$, $p<0{\cdot}0001$). They were more likely to have tried drugs; 19% had sniffed glue compared with 2% of the non-smokers ($\chi^2=52{\cdot}45$, $p<0{\cdot}0001$), and 29% had tried other drugs compared with 4% of the non-smokers ($\chi^2=77{\cdot}43$, $p<0{\cdot}0001$). The overall incidence of glue sniffing was 5%—4% of the girls and 7% of the boys. Nine per cent of all the children had tried taking other drugs—7% of the girls and 11% of the boys.

Drinking alcohol was common among the children; 95% had had an alcoholic drink at some time, 43% had had one within the last week, and 30% drank regularly every week. Overall, smoking was no more common among those children who drank than those who did not drink. Forty per cent had had their last drink at home.

There was no difference between the sexes in the overall numbers who had tried alcohol, but significantly more boys than girls—43% compared with 23%—had first had alcohol when they were less than 10 years old ($\chi^2=27{\cdot}82$, $p<0{\cdot}0001$), and more boys were drinking regularly every week—37% compared with 22% ($\chi^2=15{\cdot}49$, $p<0{\cdot}001$).

### WEIGHT PROBLEMS

There were differences between the sexes in their perception of whether they had a weight problem (18% were overweight and 7% underweight). Girls were significantly more likely to see themselves as overweight ($\chi^2=25{\cdot}30$, $p<0{\cdot}0001$). The sexes were equally divided in their perception of being underweight.

### OTHER PROBLEMS

Twelve per cent of the children had had glandular fever, 22% felt there was something wrong with their eyes but only 13% wore glasses. Half of those who did not wear them also did not like the idea of having to wear them. Twenty eight per cent were wearing or had worn braces on their teeth and half of these did not mind wearing them. Exactly three quarters of all the children had had fillings

Appreciation of other peoples' smells rated high; 92% noticed other peoples' bad breath, and 56% their smelly feet They were, however, less conscious of their own halitosis, with 58% worrying that their own breath smelt, and 44% that their feet were smelly. There were no differences between the sexes in this group.

WHO WAS TURNED TO FOR ADVICE

Parents were first turned to for advice about illness by 36% of the children. Mothers were a more popular choice (77%) than fathers (5%), with more girls than boys (85% compared with 70% consulting their mothers), and more boys than girls (7% compared with 3%) consulting their fathers. Only 4% first consulted a friend (7% of the girls and 2% of the boys), 4% consulted a doctor first (1% of the girls and 7% of the boys) and less than 1% asked a teacher

ATTITUDES TO HEALTH

Only 13% agreed with the statement that, 'What happens to your health is a matter of luck', perhaps because 85% agreed with the statement that, 'There are many things that you can do to be healthy and avoid illness'. Three quarters felt that good health was largely due to sensible living, and 82% felt that each person should look after their own health. To the statement, 'If you wait long enough you will get over most illnesses' about a third agreed, a third disagreed, and a third did not know.

Modern medicine seemed to be popular, with only 10% thinking that old fashioned remedies were better, and the remainder either disagreeing (51%) or not knowing (39%).

Given that most children seemed to think that their health was in their own hands it was interesting to look at their diet after school. They were asked what they had eaten and drunk the previous day between leaving school and going to bed. Tables 5 and 6 give these results.

Table 5 *Foods eaten after school*

| *Food* | *No of children (%)* |
|---|---|
| Meat, sausages, and pies | 380 (60) |
| Vegetables | 308 (48) |
| Sweets and chocolate | 290 (45) |
| Bread | 282 (44) |
| Crisps | 229 (36) |
| Biscuits | 224 (36) |
| Fruit | 210 (35) |
| Chips | 173 (27) |
| Cereals | 143 (18) |
| Sandwiches | 104 (16) |
| Cakes | 92 (15) |
| Fish | 85 (13) |
| Beans and pulses | 77 (12) |
| Cheese | 76 (12) |
| Ice creams | 74 (12) |
| Eggs | 70 (11) |
| Salads | 67 (10) |
| Yogurt | 41 (6) |
| Rice | 41 (6) |
| Spaghetti | 30 (5) |

Table 6 *Drinks taken after school*

| *Drink* | *No of children (%)* |
|---|---|
| Tea | 364 (56) |
| Carbonated flavoured drinks | 310 (48) |
| Coffee | 295 (46) |
| Water | 250 (39) |
| Milk and shakes | 244 (38) |
| Orange squash | 237 (37) |
| Fruit juice | 113 (18) |
| Alcohol | 89 (14) |

Sport is now regarded by our society as a healthy activity and the children were asked their main reasons for taking part in sports; 60% said they did because they enjoyed it, 9% because it was healthy, 16% because they had to, and 11% because they thought it was both enjoyable and healthy. The only difference between the sexes was in the statement, 'Because we have to', and significantly more girls than boys answered affirmatively ($\chi^2=9{\cdot}27$, $p<{\cdot}01$).

## Discussion

This age group is traditionally considered to be relatively healthy, making few demands on medical resources and showing little interest in their own health[3]; their most common worries are about unemployment, self confidence, and academic aspects of schools.[4] The first of these propositions does seem to be borne out in the present study, with only 1% considering themselves to be in poor health. This, however, did not include the 72 children who were away on the day the questionnaires were given, possibly because of illness. What the children actually meant by 'health' is, however, difficult to ascertain as about three quarters of the sample said that they had taken medicine in the previous four weeks; three quarters suffered from headaches, and if one extends health problems to include teeth, three quarters had had fillings. In addition, one third of the children in the study drank alcohol at least once a week, got depressed every day (or at least once a week), had had time off school in the previous four weeks because of illness, or had visited their doctor in the previous three months. Futhermore, 19% were taking medicine at the time of the questionnaire, and a quarter had had an accident or injury in the previous month.

It therefore seems probable that 'health' defined by the *Oxford Dictionary* as '(1) soundness of body; that condition in which its functions are duly discharged, or (2) spiritual, moral, or mental soundness'—is to these children an overall concept of wellbeing which is unaffected by relatively minor ailments such as headaches or asthma when considered from day to day. Nevertheless, children's concepts of actual health problems would appear to be much the same as adults because when asked specifically about breathing problems like asthma the rate cited by the children themselves was almost exactly the 11% reported in a recent survey of parental attitudes.[5] An interesting future study would be to find out whether parents' and children's classifications of other conditions are also identical.

A further parallel with adults is that the differences between sexes in rates of consultation with the family doctor and in the use of medicines seem to be clearly established by around 15 years of age.[2 6]

Prevention of illness by health education is medically fashionable, and in some ways health educators can take heart from the fact that not only did the children appear well informed on health matters, but they also thought that they were responsible for, and had power over, their own health. Despite these attitudes the dilemma remains that people do not necessarily act on what they know. Information by itself is only one small step towards change; it is how and whether it impinges on the many other factors in peoples' lives, like their age, their priorities, and their social circumstances, that also play a part.

This is highlighted by the complex interplay between smoking, alcohol consumption, and drug taking among teenagers. Thus although almost all the children knew the risks of smoking, one in five, at the ages of 14 and 15 were smoking. Not only this, but if they smoked they were twice as likely to drink alcohol at least once a week, and seven times more likely to have tried other drugs. Alcohol intake on the other hand, as shown in other studies, was not associated with increased smoking.[7]

The message of health education does not, on superficial examination, seem to have had much effect on diet. Both what was eaten and drunk after school in most cases hardly fitted into what is nowadays regarded as healthy. Without similar information as to what this age group were eating, say five years ago, however, it would be difficult to draw any conclusions about the changes that may have taken place.

A final surprising finding was the continuing importance of the parental role (especially the mother's) at this age, and the relatively small role (in health matters), that teachers and doctors played This parental role also has its dangers, as the children may not only turn to parents for advice but they may also imitate the example they give, for instance by smoking.

Both these facts strongly suggest that the health education of the children's parents and the children themselves as future parents should be more strongly emphasised, together with the reality that bringing about important changes in health related behaviour is the result of many highly complex factors and may, if it happens at all, take a generation or more.

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# Twenty four hour intermittent, ambulatory blood pressure monitoring

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SUMMARY Blood pressure and heart rate were measured every 30 minutes during the day and every hour during the night in 43 children (20 girls and 23 boys, aged 10 to 16) with a portable automated monitor. The apparatus was better accepted in girls than in boys, and the failure rate was lower during the day. The overall failure rate was 22%, which corresponds with comparable studies in adults. During the night blood pressure and heart rate fell by 10% and 14% of the daytime values, respectively. Mean (SD) blood pressure was significantly higher in boys than in girls (125/72 (17/8) *v* 109/64 (9/5) mm Hg) and measurements correlated positively with age, body weight, and height of the subjects. Heart rate was not significantly influenced by gender or age. A positive correlation between heart rate and blood pressure was found when expressed as standard normal deviations of hourly variations. In children intermittent monitoring of ambulatory blood pressure and heart rate is a suitable method for measuring individual diurnal patterns.

Intermittent, ambulatory 24 hour blood pressure and heart rate recording is increasingly used in adults for diagnostic and therapeutic purposes [1] A circadian rhythm has been shown, with its nadir in the early morning hours, a bimodal curve during the day, and peaks in the late morning and early evening hours.[1–3] This rhythm remains constant and is sometimes even enhanced in benign hypertension; other conditions such as pregnancy associated hypertension, malignant hypertension, pheochromocytoma, autonomic neuropathy, and some depressive disorders may affect it.[1–3] Casual office or clinic readings are higher than values obtained by ambulatory blood pressure and heart rate devices, and recent data suggest that cardiovascular risks are more accurately predicted by ambulatory blood pressure readings.[1] This technique is often used in the evaluation, diagnosis, and treatment of hypertension and the evaluation of hypotensive states and syncopes.

Intermittent, ambulatory 24 hour blood pressure and heart rate recording has not been used in children until now, mainly for technical reasons. The first available devices measured blood pressure and heart rate intra-arterially thus practically preventing their use in children. The first non-invasive technology was semiautomated, and required the patient to activate the cuff with an inflation bulb; a considerable degree of patient cooperation was essential to allow such a device to be effective. Another disadvantage was that no readings could be obtained while the subject was asleep.[3–5] We report here the results of intermittent, ambulatory 24 hour blood pressure and heart rate recordings in a relatively small sample of volunteer children, using a fully automated device, developed by Instruments for Cardiac Research. Validation studies in normotensive or hypertensive adults showed good agreement between this and other non-invasive systems with simultaneous intra-arterial or mercury sphygmomanometric determination, and a fairly good patient acceptance and reproducibility.[1 3 6 7]

## Subjects and methods

Forty three volunteers, 20 girls and 23 boys, with a median age of 13½ years (range 10 to 16) were investigated. All were healthy and were not taking any drugs (including hormonal contraception) The ranges of body weight and height were 31 to 64 kg (mean 44·5) and 1·47 to 1·67 m (mean 1·57) for girls and 28 to 69 kg (mean 48·2) and 1·43 to 1·83 m (mean 1·61) for boys. The body mass index, calculated by dividing the body weight by the height squared, ranged from 13·1 to 26·0 kg/m$^2$ (median 18·2) in boys and from 14·0 to 22·7 kg/m$^2$ in girls (median 17·9). The pubic hair development of the boys ranged from prepubertal to stage 5 according to Tanner (median stage 3). The pubic hair development of the girls was not assessed The boys were recruited in a nearby school and seen on a regular school day (when there was no gymnastic lesson or other sporting activity) in the outpatient clinic where the monitor and the questionnaire were explained and a short clinical examination was performed. Unfortunately, it proved difficult to recruit sufficient girls from the same source, therefore girls from another school were enrolled in the study and for logistic reasons the measurements were performed during the weekend at their homes.

The recorder, SPM 5200 (weight 1·6 kg), was hung over the shoulder by means of a comfortable strap. The apparatus consisted of the inflating pump with its batteries, a microprocessor controlling inflation and deflation of the cuff, and a storing unit for the blood pressure and heart rate readings. If Korotkov sounds were not detected accurately by the piezoelectric microphone the system reverted automatically to an oscillometric recording method. The first and the last sound were taken as systolic and diastolic blood pressures, respectively. Mean blood pressure was calculated as the sum of the diastolic plus one third of the pulse pressure. Conditions preventing measurement within 90 seconds and measurement failure due to excessive noise production or battery failure were indicated by code on the visual display. A more detailed description of the system is given by Turm and Graney.[3] The monitor was programmed to measure blood pressure and heart rate every 30 minutes from 6.00 am to 5.59 pm (day) and every 60 minutes from 6.00 pm to 5.59 am (night). To increase the number of available blood pressure and heart rate readings and the motivation of the children to enter the study they were allowed to take additional measurements by operating a manual control switch. Exceptionally, programmed measurements could be manually cancelled and postponed if they occurred at a time when it was impossible for the child to hold his or her arm in a suitable position for measurement. The time spent in bed and inconvenience caused by the apparatus were assessed from a questionnaire. Seventeen of the 23 boys started monitoring between 3 pm and 5 pm. in all other subjects the time of starting the 24 hour registration was evenly distributed over the day. The cuff was attached to the non-dominant arm with the microphone taped over the brachial artery. Cuff size was 8 or 12 cm in width, according to the recommendations of Leumann *et al*[8] Measurements that produced a systodiastolic blood pressure difference of less than 20 mm Hg were regarded as erroneous and therefore not used for further analysis. Simultaneous mercury column and monitor readings on opposite arms were performed in 12 boys. No significant difference between the two methods was found; the mean differences were 0·45 mm Hg (−5·5 to +6·5) for systolic blood pressure and −2·0 mm Hg (−6·5 to −4·5) for diastolic blood pressure. No calibration on the individual subject was performed.

The data obtained from the recorder, the statements from the questionnaires, and the clinical data were analysed by the software package SAS, version 5·08 (SAS Institute Inc, Cary, North Carolina, United States). Analysis of variance, based on general linear models, was applied to study the influence of age, body weight, height, body mass index, and sex of the subjects, and of day, night, bed, or hook up time on the 24 hour course of blood pressure and heart rate. The coefficients of variation for nocturnal and diurnal blood pressure or heart rate were calculated separately. The interaction between blood pressure and heart rate was studied by relating absolute values, standard normal deviations,[9] and hourly differences. The circadian rhythm of blood pressure or heart rate was mathematically assessed using a cosine function[10] and Fourier analysis. Significance was assumed when $p<0·05$.

## Results

The acceptance of the apparatus was very good during the day; a considerable inconvenience was reported only when the children played sport and dressed and undressed. One girl and three boys were particularly disturbed by the weight of the monitor. Inconveniences were more pronounced in bed. Four boys removed the cuff because they could not fall asleep and 17 boys and 10 girls woke up, most of them repeatedly, when the cuff was inflated. Of the measurements 22% (boys 25%, girls 18%) were incomplete. 50% of these were due to the fact that the measurement could not be completed within 90 seconds; this might have been caused by improper placement of the cuff, loose connections between cuff and monitor, or an air leak in the system. In 25% excessive noise was produced due to movements of the arm; battery failure ocurred only once (2%). The remaining 23% of the failed determinations were without explanation. In addition to the incomplete readings, 2·3% of measurements were deleted because the difference between systolic and diastolic blood pressure was less than 20 mm Hg. Almost all readings (97%) were performed by the auscultatory method. The boys stopped and restarted a considerable number of the measurements with the manual control switch: 22% of the total measurements were cancelled; 36% of the finally performed readings had been triggered

Table *Mean (SD) values of blood pressure and heart rate recorded over 24 hours and separately of day and night in 20 girls and 23 boys*

| | *Blood pressure (mm Hg)* | | | *Heart rate (beats/minute)* |
|---|---|---|---|---|
| | *Systolic (mean (SD))* | *Diastolic (mean (SD))* | *Mean* | |
| 24 Hours | | | | |
| All | 118 (16) | 68 (7) | 85 (9) | 81 (7) |
| Girls | 109 (9) | 64 (5) | 79 (5) | 80 (7) |
| | $p<0\cdot001$ | $p<0\cdot001$ | $p<0\cdot001$ | |
| Boys | 126 (17) | 72 (8) | 90 (9) | 81 (7) |
| Daytime | | | | |
| All | 123 (18) | 71 (7) | 88 (9) | 85 (8) |
| Girls | 113 (11) | 68 (5) | 83 (5) | 86 (7) |
| | $p<0\cdot001$ | $p<0\cdot001$ | $p<0\cdot001$ | |
| Boys | 130 (21) | 74 (8) | 93 (11) | 86 (8) |
| | $p<0\cdot001$ | $p<0\cdot001$ | $p<0\cdot001$ | $p<0\cdot001$ |
| Night time | | | | |
| All | 110 (12) | 64 (10) | 79 (9) | 75 (9) |
| Girls | 102 (7) | 60 (6) | 74 (6) | 73 (7) |
| | $p<0\cdot001$ | $p<0\cdot001$ | $p<0\cdot001$ | |
| Boys | 117 (14) | 68 (12) | 85 (11) | 75 (9) |

manually. By contrast, in girls only 2% of the measurements were cancelled and 17% manually triggered.

The table shows the mean values of blood pressure and heart rate recorded over 24 hours and separately during the day and night. A significant sex difference was noted with regard to blood pressure ($p<0\cdot001$) but not for heart rate. Systolic, mean, and diastolic blood pressure, and heart rate were appreciably lower ($p<0\cdot001$) during the night compared with diurnal readings. In girls the mean nocturnal blood pressure and heart rate were 11% and 13% lower, respectively, than diurnal recordings. The corresponding nocturnal decreases for boys were 9% and 15%, respectively. The coefficient of variation (mean (SD)) for systolic, mean,

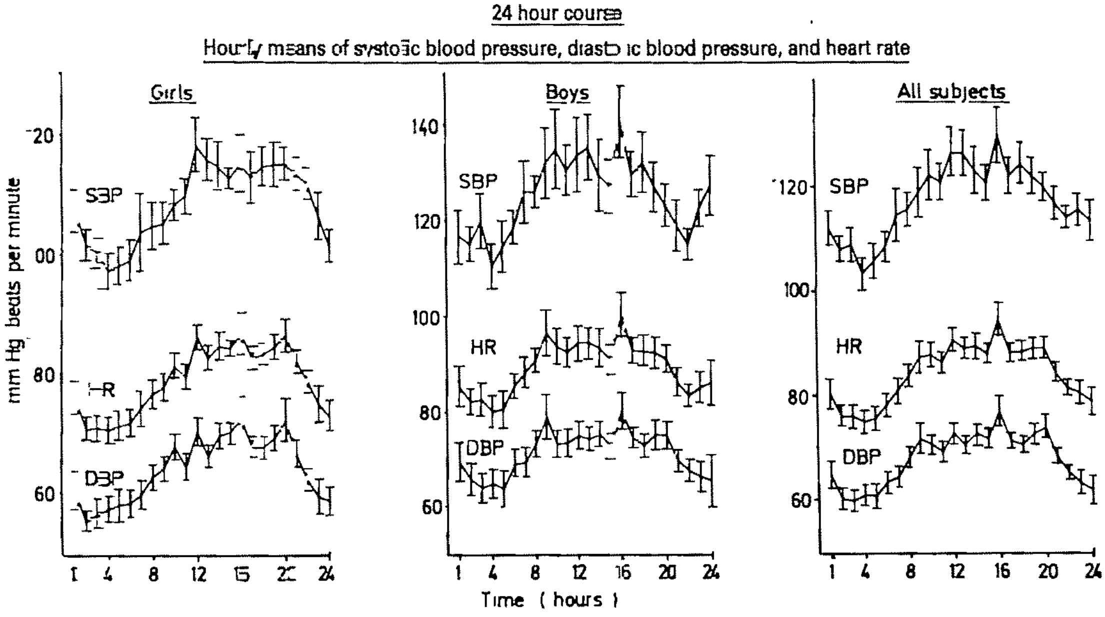

Fig 1 *Hourly blood pressure and heart rate recordings during 24 hours in 20 girls and 23 boys.*

and diastolic blood pressure, and for heart rate were 11·0 (5)%, 10·6 (5)%, 13·7 (6)%, and 20·5 (7)% during the day, and 11·1 (5)%, 11·2 (4)%, 15·5 (6)%, and 20·9 (11)% during the night. No difference was observed between girls and boys.

When studied by analysis of variance, systolic, mean, and diastolic blood pressure and heart rate were significantly influenced by whether the readings were taken during the day or night and by whether the subjects were in bed ($p<0·001$). Sex, age, body weight, and height influenced blood pressure measurements ($p<0·001$) but not heart rate. The time of starting the 24 hour recording significantly influenced the course of heart rate in boys ($p<0·05$) but not in girls; its influence on blood pressure was not significant. The correlation between absolute values of heart rate and systolic, mean, and diastolic blood pressure was not significant. A positive and significant correlation between heart rate and blood pressure, however, was found using standard normal deviations ($p<0·001$) or the hourly variations ($p<0·05$) No correlation was found between body mass index and blood pressure or heart rate

Fig 1 shows the course of the hourly mean (SEM) values of systolic and diastolic blood pressure and heart rate over 24 hours. Systolic and diastolic blood pressure and heart rate reached their nadir at about 4.00 am, increasing thereafter to a first peak around mid-day. In the early afternoon a slight decrease occurred, after which a second peak was attained. In the boys blood pressure and heart rate values peaked at 4.00 pm, while the course in the girls was smoother. The fitting of a cosine function to the course of the mean hourly values of systolic and diastolic blood pressure and of heart rate (fig 2) showed a good synchronisation of systolic and diastolic blood pressure, with changes in the heart

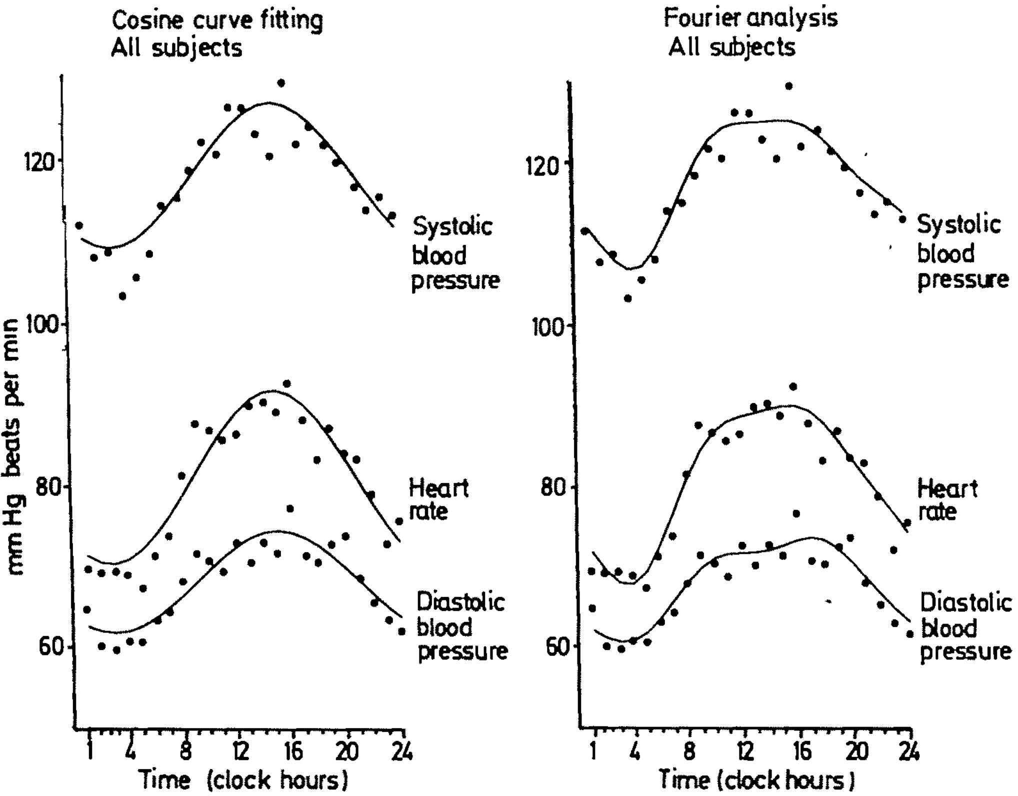

Fig 2 *Mathematical transformation of the 24 hour values for systolic and diastolic blood pressure and heart rate in 43 children The left panel shows the cosine curve fitting. The corresponding formulae, in which t signifies the hour of the day, are. systolic blood pressure*$=118+8{\cdot}8\cos(t+2{\cdot}3)$; *diastolic blood pressure*$=68+6{\cdot}3\cos(t+2{\cdot}3)$, *heart rate* $=81+10{\cdot}6\ (t+2{\cdot}4)$ *The right panel shows the Fourier analysis The corresponding formulas are systolic blood pressure*$=118-6{\cdot}2\cos t-6{\cdot}1\sin t+1{\cdot}4\cos 2t-1{\cdot}3\sin 2t+0{\cdot}7\cos 3t+0{\cdot}8\sin 3t$, *diastolic blood pressure*$=68-4{\cdot}5\cos t-4{\cdot}4\sin t-0{\cdot}4\cos 2t-1{\cdot}3\sin 2t+0{\cdot}2\cos 3t+0{\cdot}5\sin 3t$; *heart rate*$=81-8{\cdot}0\cos t-7\ 2\sin t+0{\cdot}6\cos 2t-1{\cdot}9\sin 2t+0\ 8\cos 3t+0{\cdot}5\sin 3t$

rate slightly preceding those in blood pressure. A slightly better approximation of the circadian rhythm could be achieved using a Fourier analysis.

## Discussion

When compared with other widely available automated recorders, the Instruments for Cardiac Research monitor SPM 5200 has the advantage of a relatively low weight and low noise production. It does not need electrocardiographic leads for the registration of heart rate and displays error codes rather than artefactual readings.[5-7] All these characteristics make this monitor a suitable recorder for measuring ambulatory blood pressure in children, and for this age group it is probably the only suitable device for recordings during the night.

The main purpose of the present study was to test the patient acceptability and the failure rate of 24 hour recording with this portable device. Only a limited validation of the system and no individual calibration were performed. The accuracy of these measurements remains uncertain, and further trials using children are required. Any validation procedure carried out at only one point in time, however, will not necessarily reflect the conditions prevailing over 24 hours in children of this age group. In the present study acceptance was worse and the failure rate higher than those reported in studies in adults[4] or in children that had been performed only during the day.[5] Acceptance as well as failure rates were comparable, however, with results reported in adults who were studied during a full 24 hour period.[11] Patient acceptance was better and the failure rate lower in girls, who manually operated the monitor less frequently. More pronounced physical activity and a greater interest in the apparatus in boys might account for this difference.

The children reported here maintained a circadian pattern of blood pressure and heart rate, which corresponded with the sleep-wakefulness cycle. This cycle could be analysed by a cosine function, as previously advocated by Halberg.[10] A slightly better approximation could be achieved using a Fourier analysis, which better reflects the plateau of blood pressure and heart rate that occurs from the late morning to the early evening hours. In older healthy subjects or patients with essential hypertension blood pressure and heart rate showed a comparable circadian rhythm.[2 3 11] In adults the circadian rhythm of blood pressure parallels that of heart rate and plasma concentrations of noradrenaline, suggesting that changes in sympathetic tone control the diurnal changes in blood pressure.[11] Plasma noradrenaline concentrations were not assessed in our group of children; we found, however, that as in adults the changes in heart rate correlated significantly with those in blood pressure. The circadian pattern in blood pressure might, therefore, be strongly influenced by the sympathetic nervous system in children as well as in adults.[12] Blood pressure increases before waking up; and this has led to the assumption that a true inherent rhythm in blood pressure might exist, though with the influence of sleep and activity superimposed.[10]

Blood pressure was higher in boys than in girls and correlated positively with the age, body weight, and height of the volunteers, confirming data from casual blood pressure readings.[13 14] As girls were studied when not at school and boys on a school day one might assume that stress related to the school activity increased the sympathetic tone and consequently the blood pressure in boys. The absolute values of heart rate, an index of sympathetic nervous tone;[11 12] the variability of heart rate, as judged by its standard deviation or coefficient of variation; the 24 hour course of heart rate, and the relation between heart rate and blood pressure were comparable in both sexes thereby arguing against such an explanation. The heart rate pattern was also independent of age, body weight, and height; sympathetic mechanisms do not fully explain the influence of age, body weight, and height on blood pressure. Differences in the composition of the body water compartments might be a more likely explanation for the influence of sex, age, and height on blood pressure.[15] The time of starting the 24 hour recording significantly influenced the course of heart rate in boys but not in girls. This difference is probably related to the setting in which the investigation was begun—namely, familial home environment for the girls and a hospital outpatient clinic after the examination of pubertal status for the boys. In the present study no correlation was found between body mass index and blood pressure. This finding does not question the well recognised link between overweight and high blood pressure: all our subjects were lean with a body mass index of less than 30 kg/m$^2$.[16 17]

As in adults the most obvious uses of this newly available technique in children may be the evaluation of borderline hypertension and the efficacy of antihypertensive drug regimens.[1] Another use might be research in essential hypertension, a common condition in adults that probably starts early in life and is influenced by familial factors. Now that the great diurnal variability of blood pressure is beginning to be appreciated it is somewhat surprising that isolated clinic, office, or home measurements have been such good predictors for the risk associated with a high blood pressure. Some recent investigations suggest, however, that hypertensive target organ damage, including left ventricular hypertrophy or retinopathy, correlates better with 24 hour blood pressure measurements and especially with measurements taken during work than with those taken outside work.[1] Left ventricular hypertrophy has been observed not only in adolescents with borderline essential hypertension but also in the offspring of hypertensive families. As the degree of heart hypertrophy correlates only weakly with isolated blood pressure measurements an interplay of more factors than the simple increased blood pressure load has been suggested to explain the myocardial response to hypertension. In this context ambulatory 24 hour monitoring of blood pressure in normotensive children of hypertensive families might uncover new determinants of heart hypertrophy.[18] It has been shown, by invasive methods, that patients with established or borderline essential hypertension, as well as young normotensive adults with a positive family history for essential hypertension, often present a changed pressor response to sympathetic stimulation.[19] The ambulatory recording technique for blood pressure, as used in this study, might become a useful non-invasive tool for further investigation of the relation between blood pressure and the sympathetic nervous system in children as well as in adults. In contrast with other clinical variables like body weight, height, and blood lipids, casual measurements of blood pressure rarely follow individual centiles over time.[13 16] This finding might be explained at least in part by the great diurnal and individual variability of the blood pressure that occurs naturally. Multiple measurements of blood pressure over one day might possibly lead to more conclusive results and detect children at risk of becoming hypertensive adults. In this context ambulatory 24 hour monitoring of blood pressure in children has already been advocated.[17–20]

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# Plasma renin activity in infants with congenital heart disease

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SUMMARY Plasma renin activity was estimated in 11 infants with severe congestive heart failure. The infants had congenital heart disease with left to right shunts and were receiving diuretic treatment. Plasma renin activity was measured by radioimmunoassay of generated concentrations of angiotensin I. The mean (SD) plasma renin activity was 84 (21) ng angiotensin I/ml/hour, which is considerably above normal infant values. A hyperactive renin-angiotensin system may be detrimental in these patients. Angiotensin converting enzyme inhibitors may be of value in treating infants with severe congestive heart failure.

The advent of angiotensin converting enzyme inhibitors for the treatment of congestive heart failure has stimulated interest in how they affect the renin-angiotensin-aldosterone system. Adults, who have congestive heart failure due to myocardial disease, have been found to have raised plasma renin activity and plasma aldosterone concentrations after the acute phase of myocardial failure but these become less as the heart failure becomes chronic.[1]

Infants with congestive heart failure on diuretic treatment often have a disturbed electrolyte balance, especially if they are failing to thrive and are receiving maximum medical management; and it seems likely that such disturbance would have an effect on the renin-angiotensin-aldosterone system. We report a study of the plasma renin activity in infants with congenital heart disease and congestive heart failure.

## Patients and methods

We studied 11 infants with an age range of 14 to 84 days (mean 38 days). All were term babies except one born at 36 weeks' gestation. Their mean (SD) weight was 2320 (660) g at the time of the study. Patients were selected if they had congenital heart disease with predominantly left to right shunts, high pulmonary blood flow, and no obstruction in the systemic circulation (for example, coarctation). The infants studied comprised three with a ventricular septal defect, six with complete atrioventricular septal defect, one with double outlet right ventricle, and one with truncus arteriosus (type I). They all had sufficiently severe congestive heart failure that they were failing to thrive on maximal medical management and for this reason had been admitted to hospital. All infants were taking frusemide and digoxin, and all but one were taking amiloride. Informed parental consent was obtained before taking the blood specimens; these were taken only when there was a clinical need for plasma electrolyte estimation.

Plasma renin activity was measured after the babies had spent a minimum of seven days in hospital receiving treatment for heart failure. The age of the infant, gestational age at birth, weight, diuretic and other drug treatment, cardiac diagnosis and feed content and volume were recorded. On the day of measurement for plasma renin activity the heart rate, respiratory rate, and blood pressure while resting (quiet or asleep) were measured. The systolic blood pressure was recorded with a standard sphygmomanometer, with a cuff that covered at least two thirds of the right upper arm, and a pulse Doppler device. The diastolic blood pressure was recorded from an automated blood pressure machine (Dynamap) using the diastolic value corres-with the systolic value that most closely matched the systolic pressure obtained manually.

Plasma renin activity was measured, while the infant was supine, between two and three hours after the infant's last feed between 9 and 10 am. Blood was obtained from a peripheral vein, allowing blood to drip from a needle into a chilled tube containing edetic acid as an anticoagulant. The sample was transferred on ice to the laboratory for immediate cold centrifugation; the supernatant was separated and stored at −20°C until analysed. One ml of whole blood was required for the angiotensin I assay: blood was taken for packed cell volume estimation and plasma sodium, potassium, urea, and creatinine concentrations at the same time. A urine specimen collected at roughly the same time as the blood sample was similarly analysed

Plasma renin activity was assessed by the concentrations of angiotensin I generated at 37°C and pH 6·0; this was measured by radioimmunoassay in an antibody coated tube and calibrated against the Medical Research Council standard 71/328 (Kit SB-REN-2, CIS (UK) Ltd, High Wycombe, United Kingdom). All analyses were carried out in duplicate in the same batch; the mean intrabatch variation was 5·3%. Results are expressed as angiotensin I generated in ng/ml/hour. Included in the assay for comparison were five infants age 10–47 days who were expected to have normal values. These patients comprised two babies admitted because of cyanotic spells and subsequently found to be normal, one infant with a cleft palate, and two convalescent infants—one after repair of ileal atresia and the other after streptococcal peritonitis. All had normal plasma urea and creatinine concentrations.

## Results

The mean plasma renin activity was 84 ng angiotensin I/ml/hour (SD 21; range 57–126). The mean (SD) concentration of plasma sodium at 132 (3·8) mmol/l was marginally low, and the range of urinary sodium concentration was from 6 to 110 mmol/l (median 33). The mean concentrations of plasma potassium, urea, and creatinine were within normal ranges. There was no correlation between plasma renin activity and plasma sodium, potassium, urea, or creatinine, or for urinary sodium, sodium: creatinine ratio; or sodium intake for the preceding 24 hours. Neither was there any correlation between plasma renin activity and age, weight, blood pressure (systolic or diastolic), packed cell volume, or dose and duration of diuretic; similarly, there was no correlation with degree of tachypnoea or tachycardia.

The infants who were expected to have normal values for plasma renin activity ranged from 5·2–31 ng angiotensin I/ml/hour (mean 19·6; SD 10·5). The plasma renin activities for the study group were significantly higher than those of the normal group ($p<0{\cdot}001$; Student's $t$ test)

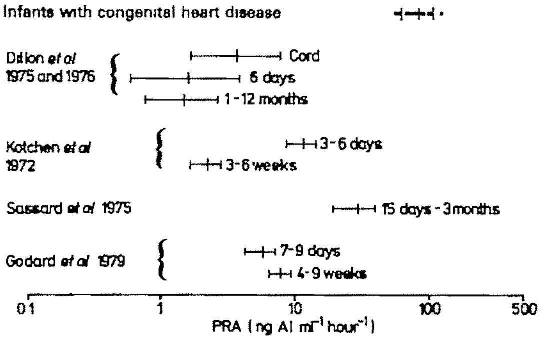

Figure *Plasma renin activity plotted on a logarithmic scale for patients with congenital heart disease with reference normal values (mean SD) from previous publications.*[2–6]

## Discussion

The figure shows that the mean plasma renin activity in infants with heart failure is considerably above previously reported normal mean values for newborns and infants and falls outside normal ranges quoted for infants.[2–6] In only one series, in which the normal population was a group of inpatients 15 days to 3 months old with benign adenoiditis, does the range overlap.[5] Our 'normal' patients could conceivably have had conditions which might have influenced their renin activity; none the less, their plasma renin activity values were within previously reported normal ranges. Orally administered frusemide is known to produce an acute rise in plasma renin activity in normal infants,[7] but the figures reported were considerably below the range of values in our infants.

We have not found any correlation between any of the variables assessed and the plasma renin activity. In normal infants the correlations have been confined to a variable decline in the plasma renin activity from the time of birth until 9 years of age and, in one report, a correlation was found with salt intake and urinary osmolality.[6] The absence of correlations with factors known to influence renin activity may be related to the large numbers of relevant variables present in this small group of patients—for example, diuretics, blood volume, sodium balance, potassium, hypoxia, and age. No likely trends were observed, however, with individual variables; this gives no indication that expanded numbers in this study would have provided significant correlations.

Our results indicate that the renin-angiotensin-aldosterone system is hyperactive in this group of patients; this may be attributable to the congestive heart failure or to the treatment given. The question as to whether the response is appropriate cannot be answered at this stage. What may be an appropriate response in a subject with normal anatomy and physiology may be inappropriate in an infant with major disturbances in communications between systemic and pulmonary circulations and a myocardium under stress.

It has been reported that plasma renin activity parallels angiotensin II concentrations in infancy.[8] Angiotensin II is a potent vasoconstrictor contributing to the afterload on the left ventricle. Reduction of afterload has been shown to be beneficial in congestive heart failure.[9, 10] It may be that angiotensin converting enzyme inhibitors are an appropriate method of directly reducing the afterload by the removal of vasoconstrictive forces associated with a high plasma renin activity (and presumably angiotensin II) in infant heart failure.

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# Hyperkalaemia, cardiac arrhythmias, and cerebral lesions in high risk neonates

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SUMMARY The case notes of 20 infants with hyperkalaemia (defined as two successive serum potassium measurements of >7·5 mmol/l) were reviewed. The incidence of hyperkalaemia was also looked at in an unselected population of 200 low birthweight infants. The mean gestational age of the 20 affected infants was 29 weeks and the mean birth weight 1235 g. The incidence of hyperkalaemia in the cohort of 200 infants weighing less than 1500 g at birth was 3·5%. Hyperkalaemia was associated with a high incidence of cardiac arrhythmia (60%), impaired renal function (50%), and changes on cerebral ultrasonography (88%). Hyperkalaemia responds slowly to conventional treatment with dextrose, insulin, and exchange resins. There is a close temporal relation in some infants between hyperkalaemia and cardiac arrhythmias and periventricular leukomalacia, suggesting a causal association.

There are little published data on the incidence and consequences of neonatal hyperkalaemia. It is known to cause cardiac arrythmias,[1–4] and recent evidence suggests that increased potassium concentrations in cerebrospinal fluid or brain parenchyma may cause spasm of the intracerebral arteries.[5] Both these factors could impair the neonatal cerebral circulation.

We looked at the incidence of hyperkalaemia in an unselected population of very low birthweight infants (n=200), and reviewed the case notes of 20 infants known to have had hyperkalaemia to estimate the incidence of cardiac arrhythmia, renal impairment, and cerebral abnormality.

## Methods

A computer search for cases of hyperkalaemia among all admissions to the neonatal unit from April 1983 until May 1986 was undertaken. Hyperkalaemia was defined as two sequential serum potassium measurements of 7·5 mmol/l or more in non-haemolysed samples. In an earlier study at the Leicester Royal Infirmary and Nottingham City Hospital neonatal units 200 consecutive very low birthweight infants had had their neonatal complications documented prospectively. Serum potassium concentrations were recorded and from these data we calculated the incidence of hyperkalaemia in this group of very low birthweight infants.

The biochemical data were obtained in all the infants with hyperkalaemia. High serum urea or creatinine concentrations were defined as those above the normal range given in published reports.[6 7] Twelve hourly arterial pH measurements before and during the hyperkalaemic episodes were recorded to assess the degree of acidosis. We assessed the duration and severity of hyperkalaemia by calculating in mm$^2$ the area under the curve that

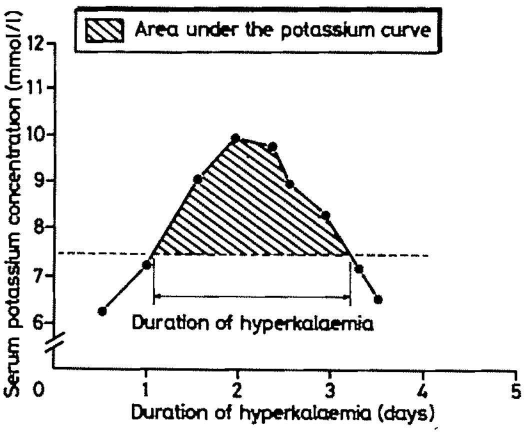

Fig 1 *Method of calculating duration and severity of hyperkalaemia (serum potassium concentration of >7·5 mmol/l)*

Table *Details of 20 infants with hyperkalaemia studied*

| *Case No* | *Gestational age (weeks)* | *Birth weight (g)* | *Age at onset of hyperkalaemia (hours)* | *Severity of hyperkalaemia (mm²)* | *Maximum potassium concentration (mmol/l)* | *Arrhythmia* | *Ultrasound findings* | *Outcome* |
|---|---|---|---|---|---|---|---|---|
| 1 | 29 | 940 | 4 | 8 | 7·7 | Bradycardia | Bilateral cystic periventricular leucomalacia | Died at six months (cot death) |
| 2 | 33 | 2100 | 24 | 28 | 8·2 | Supraventricular tachycardia, bradycardia | Not done | Survived |
| 3 | 26 | 950 | 12 | 60 | 9·4 | Supraventricular tachycardia | Germinal matrix haemorrhage | Survived |
| 4 | 26 | 970 | 24 | 100 | 8·5 | Supraventricular tachycardia | Germinal matrix haemorrhage | Died aged six days |
| 5 | 31 | 1700 | 24 | 260 | 8·8 | Supraventricular tachycardia | Normal | Died aged three days |
| 6 | 26 | 780 | 28 | 325 | 9·9 | Bradycardia | Intraventricular haemorrhage, periventricular leucomalacia | Died aged nine days |
| 7 | 25 | 700 | 12 | 350 | 12·5 | Supraventricular tachycardia | Intraventricular haemorrhage | Survived, development normal at 18 months |
| 8 | 27 | 1000 | 36 | 360 | 8·6 | Bradycardia | Germinal matrix haemorrhage; periventricular leucomalacia | Died aged seven days |
| 9 | 26 | 740 | 48 | 375 | 9·1 | Nodal arrhythmia | Germinal matrix haemorrhage, periventricular leucomalacia | Died aged twelve days |
| 10 | 28 | 1300 | 42 | 520 | 9·9 | Supraventricular tachycardia | Germinal matrix haemorrhage; periventricular leucomalacia | Survived |
| 11 | 37 | 1420 | 46 | 1308 | 12·6 | Supraventricular tachycardia | Transient flare | Died aged eight days |
| 12 | 25 | 900 | 24 | 1733 | 12·2 | Supraventricular tachycardia | Germinal matrix haemorrhage, periventricular leucomalacia | Died aged six days |
| 13 | 29 | 1100 | 36 | 8 | 7·7 | None | Intraventricular haemorrhage, periventricular leucomalacia | Survived, spastic cerebral palsy |
| 14 | 38 | 2900 | 48 | 12 | 7·8 | None | Normal | Died aged one day |
| 15 | 29 | 1400 | 36 | 255 | 8·9 | None | Transient flare | Survived |
| 16 | 25 | 780 | 12 | 295 | 9·5 | None | Not done | Survived |
| 17 | 28 | 1000 | 24 & 108 | 330 | 8·7 | None | Intraventricular haemorrhage | Survived |
| 18 | 26 | 850 | 24 | 475 | 12 | None | Intraventricular haemorrhage | Died aged one day |
| 19 | 37 | 2180 | 12 | 885 | 11·3 | None | Not done | Died aged three days |
| 20 | 24 | 900 | 42 | 895 | 12·7 | None | Intraventricular haemorrhage, venous infarction | Survived |

related serum potassium concentration to time (fig 1). This method has been previously used to assess the severity of acidosis.[8] The number of episodes of cardiac arrhythmia and the treatment of hyperkalaemia were recorded and cerebral ultrasound scans of the hyperkalaemic infants were also reviewed.

## Results

Seven of the 200 very low birthweight infants in the previously studied cohort developed hyperkalaemia in the neonatal period,[9] an incidence of 3·5%. We report the results from an additional 13 hyperkalaemic infants.

The mean birth weight of the 20 infants was 1230 g and the mean gestational age 29 weeks. In all the infants the hyperkalaemia became apparent within 48 hours of birth, and one infant had a second episode during the fifth day of life. The table gives details of the data on the infants. No infants had had prolonged seizures, and blood transfusions were not given in the first 48 hours of life, so these two possible causes of hyperkalaemia could be disregarded.

Serum urea concentrations were available for all 20 infants and creatinine concentrations were also available for 11 infants, of which five were abnormal. We used creatinine concentrations as an index of renal function when available, and the less reliable urea measurements in the rest In the nine infants in whom only urea concentrations were available, five were above the normal range.

Arterial pH estimations were available before and during the hyperkalaemic episode in 10 infants, and these showed that there was no obvious trend towards acidosis when the serum potassium concentrations were at their highest

Cardiac arrhythmias occurred in 12 (60%) of the infants; the most common was supraventricular tachycardia (n=7); three became bradycardic; one developed a nodal rhythm; and one had both supraventricular tachycardia and bradycardia. In four infants the arrhythmia preceded the diagnosis of hyperkalaemia. Five infants with cardiac arrhythmias had raised serum urea or creatinine concentrations, and therefore possible renal compromise. The mean peak potassium concentration in the group with arrhythmias was 9·8 mmol/l. This is the same as that found in the infants who did not have arrhythmias. The mean area under the curve in infants with an arrhythmia was 452 $mm^2$ compared with 394 $mm^2$ in those with no arrhythmia; this difference was not significant. In some infants with cardiac arrhythmia the blood pressure had been recorded continuously. In each infant with supraventricular tachycardia or nodal rhythm in whom continuous recordings of blood pressure were available there was a definite fall during the arrhythmia (fig 2).

The results of cerebral ultrasound scans were available in 17 of the infants. In two the scan remained normal throughout the neonatal period. The remaining 15 (88%), however, showed some abnormality; 11 had germinal matrix haemorrhage or intraventricular haemorrhage, and seven periventricular leucomalacia with or without germinal matrix haemorrhage or intraventricular haemorrhage. In a further two infants there were transient echodense areas in the parenchyma but these all resolved within two weeks of birth. In five infants with periventricular leucomalacia we determined the association between the diagnosis of hyperkalaemia and the onset of the lesion seen on the ultrasound scan. In three, parenchymal echodensity was first detected within 48 hours of the raised serum potassium concentration, and in another the next scan (performed four days after the onset of hyperkalaemia) showed periventricular leucomalacia for the first time. In one infant periventricular leucomalacia preceded the hyperkalaemia, and in three the ultrasound evidence of periventricular leucomalacia was seen within 24 hours of cardiac arrhythmia. The infant whose blood pressure trace is shown in fig 2 developed parenchymal echodensity within 12 hours of the documented arrhythmia. In only one infant was periventricular leucomalacia evident before the diagnosis of hyperkalaemia.

The hyperkalaemia was treated with insulin and infusion of 10% dextrose; calcium resonium enemas were given every four hours. Episodes of arrhythmia

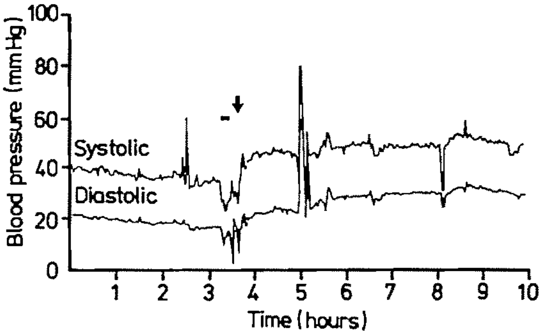

Fig 2 *Effects of supraventricular tachycardia on blood pressure in infant of 27 weeks' gestation when 24 hours old. Bar=duration of arrhythmia, terminated with 10% calcium gluconate (arrow) Systolic and diastolic blood pressures were recorded on disc every two minutes and displayed as a rolling average.*[14]

were treated with bolus injections of 0·2–0·5 ml of 10% calcium gluconate and cardioversion was not used. Case 10 (table) was treated by peritoneal dialysis

## Discussion

Despite the relatively high incidence of hyperkalaemia in the two neonatal units studied little seems to have been written about the condition in neonates. An infant is most likely to have raised serum potassium concentrations within the first 48 hours of life. At this time he or she will be receiving minimal amounts of oral or intravenous potassium, and so the likely cause of the condition is either leakage of intracellular potassium or diminished renal excretion. Potassium is predominantly an intracellular cation and any factor which causes it to move out of the cells (for example, acidosis) will result in an increased serum concentration. The rate of potassium excretion depends on the concentration gradient between the distal renal tubular cells and the luminal potassium concentration.[10] It follows that any factor increasing the intracellular potassium concentration (for example, insulin) or increasing luminal urine flow rates (for example, diuretics) will enhance potassium excretion

The most important function of potassium is to maintain the normal membrane resting potential. An increase in extracellular potassium concentration will lower the resting potential and therefore a stimulus of lesser intensity will evoke an action potential This will increase the 'excitability' of the cell membrane. An action potential is produced by the opening of sodium channels, thereby permitting the rapid entry of sodium into the cells. When potassium concentrations are extremely high these channels are inactivated and the stimulus cannot produce an electrical response.[11] This may account for the bradyarrhythmias associated with hyperkalaemia

Therefore it is not surprising that so many of the infants (60%) developed cardiac arrhythmias. Two kinds of arrhythmia predominated in our study, supraventricular tachycardia and sinus bradycardia, but many different electrocardiographic changes have been previously reported.[2–4]

Hyperkalaemia seems primarily to affect very low birthweight infants and review of the case notes of these infants showed that the most likely to suffer from it are those with other problems. Guignard *et al* showed that renal function was impaired in infants with idiopathic respiratory distress syndrome and that the degree of impairment correlated with the severity of the respiratory illness.[12] They postulated that the hypoxaemia, hypotension, or intermittent positive pressure ventilation may have been responsible. Measurements of serum urea and creatinine concentrations were available for all the infants, and 10 (50%) of them had evidence of renal impairment. This was probably the cause of their hyperkalaemia, but we were unable to identify the cause in the remainder. There may have been a reduction in renal blood flow (and therefore in distal tubular luminal urine flow) that was sufficient to impair potassium excretion but not sufficient to be reflected in raised urea and creatinine concentrations. It is more likely, however, that there was a redistribution of potassium from the intracellular to the extracellular compartments. Acidosis causes such shifts in potassium, but we did not see appreciable decreases in arterial pH during periods of hyperkalaemia.

Edvinsson *et al* showed that human cerebral arteries in vitro contract when bathed by a potassium concentration of more than 10 mmol/l.[5] They postulated that this may be partly responsible for periventricular ischaemia in neonates. Abnormalities on ultrasound scan were seen in 15 of the 17 infants (88%), of whom eight (54%) had parenchymal changes In a previous study of 200 very low birthweight infants parenchymal lesions were seen in only 14%.[9] In the present study, germinal matrix haemorrhage or intraventricular haemorrhage was seen in 70% of the infants. The close temporal relation between hyperkalaemia and periventricular leucomalacia that we found provides good circumstantial evidence of a direct association between them. In addition, three infants showed the first signs of periventricular leucomalacia within 24 hours of cardiac arrhythmia. In the case illustrated in fig 2 there was a period of acute hypotension lasting for over 20 minutes 12 hours before the first ultrasound changes of periventricular leucomalacia appeared, which supports a direct causal association between arrhythmia and cerebral infarction.

Our current policy is to treat any infant with a serum potassium concentration of >7·5 mmol/l, or a concentration of 6·5–7·5 mmol/l if it is associated with electrocardiographic abnormalities. Cardiac arrhythmias are treated with a bolus dose of 10% calcium gluconate intravenously. In the present study 13 of the infants were treated with insulin and dextrose infusions and calcium resonium exchange enemas. In these infants the mean duration of the hyperkalaemic episode was 47 hours. Because potassium concentrations decline slowly with conventional treatment we have begun to evaluate peritoneal dialysis; to date five infants have been treated in this way Setzer *et al* reported the successful treatment of neonatal hyperkalaemia by an exchange transfusion of red blood cells washed in saline.[13] Both these methods require further evaluation.

Hyperkalaemia may cause cerebral damage by reducing cerebral blood flow during episodes of cardiac arrhythmia or by inducing arteriolar spasm. In the absence of evidence to the contrary, we recommend that hyperkalaemia should be treated aggressively. Serum potassium concentrations should be checked regularly during the first 48 hours of life in very low birthweight infants, particularly in those with other problems.

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# Residual insulin secretion in adolescent diabetics after remission

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SUMMARY Twenty four hour blood glucose profiles were compared in two groups of insulin dependent adolescent diabetic patients who were beyond their initial partial remission phase. In the group with persistent endogenous insulin secretion, blood glucose profiles were significantly lower but the difference was small and not reflected in average 24 hour concentrations of glucose nor glycosylated haemoglobin. Endogenous insulin secretion must be considered in studies of metabolic control after the remission period but the effect on overall glucose control is probably clinically unimportant.

The beneficial effect of endogenous insulin secretion on metabolic control in insulin dependent diabetics has been reported.[1 2 3] Endogenous insulin may improve metabolic control because it is secreted into the portal vein and may therefore lead to improved effect of insulin on the liver. Most studies include insulin dependent patients soon after diagnosis and suggest that secretion has to be of a degree not commonly seen in adolescents after the partial remission phase. We have therefore studied the effect of the endogenous secretion of insulin after the remission phase on 24 hour glucose profiles in adolescent insulin dependent diabetics.

## Patients and methods

The 24 hour metabolic profiles of 28 patients were analysed. Two groups of adolescent insulin dependent diabetics (age range 10–17 years) were compared. All were past their partial remission phase: they did not meet the accepted criteria of an insulin requirement of less than 0·5 U/kg/day and minimal or no glycosuria, and all had had diabetes for longer than two years.[4] The patients were recruited from the clinic and were studied before any special attempt was made to improve control. The 10 patients with the highest C peptide excretion formed group A, and the 10 in whom the least was measured formed group B (table). C peptide was above the detection limit of the assay on a mean of 18 of the possible 20 occasions in group A (range 15–20) but only on a mean of one occasion in group B (range 0–3). Average 24 hour C peptide concentrations in individual patients ranged from 0·42–0·73 nmol/l in group A and from 0–0·09 nmol/l in group B.

All patients were treated with either Velosulin and Insulatard (Nordisk Ltd, Epsom, Surrey) or Actrapid and Monotard (Novo Laboratories Ltd, Basingstoke, Hants) except for one patient who was treated with Semitard and Monotard (Novo Laboratories Ltd). One patient in each group needed only one injection of insulin a day, all the rest having two.

The patients were admitted to a side ward the evening before the study. At 07 30 the following day an intravenous Teflon cannula (22G Abbocath, Abbott Ireland Ltd, Sligo, Republic of Ireland) was inserted into a forearm vein. Between samples the cannula was kept patent by flushing with saline (154 mmol/l).

A fasting sample was taken at 08 00 following which the usual morning insulin was given at 08 10.

Table *Characteristics of both groups of patients studied (means and ranges)*

| *Variable* | *Group A (n=10)* | *Group B (n=10)* | *p Value* |
|---|---|---|---|
| Age (years) | 13·7<br>(11 7–15·5) | 14·3<br>(12·0–17·0) | NS |
| Duration of diabetes (years) | 5·3<br>(2·4–10·0) | 9·5<br>(4·6–17·3) | <0·01 |
| Insulin dose (U/kg) | 1·09<br>(0·65–1·52) | 1·13<br>(0·47–1·84) | NS |
| % Total daily dose taken in morning | 66<br>(49–100) | 69<br>(47–100) | NS |
| % Morning dose as quick acting insulin | 41<br>(16–63) | 41<br>(22–56) | NS |
| $HbA_1$ (%) | 12·8<br>(10 9–14·1) | 13 2<br>(7·9–18·2) | NS |

Breakfast was eaten at 08 30, lunch at 12 15, and dinner at 18 15 with snacks at 10 30, 15 30, and 21 30. Evening insulin was given at 17 45 The diet was selected from a standard menu and had the same carbohydrate content as that prescribed for regular consumption at home. Patients were encouraged to walk about during the day. They were free to move between the floors of the hospital but rested for 10 minutes before blood samples were taken.

Blood was taken hourly on the hour during the day. Between 22 00 and 06 00 samples were taken every two hours. Finally, a sample was taken for measurement of glycosylated haemoglobin concentration ($HbA_1$).

Whole blood (1–2 ml) was mixed with 5 ml of ice cold 5% (v/v) perchloric acid (BDH Chemicals Ltd, Poole, England) in a preweighed glass tube and stored at 4°C. At the end of the study the tubes were reweighed and centrifuged. The perchloric acid extract was separated and stored at −20°C before being analysed. The remainder of the blood was placed in a plastic tube and after clotting serum was separated and stored at −20°C for subsequent measurement of C peptide secretion. Blood for measurement of $HbA_1$ concentration was collected in a plastic tube containing edetic acid.

Blood glucose concentration was measured in the perchloric acid extract by a continuous flow enzymatic fluorimetric technique.[5] Serum C peptide secretion was measured by a single antibody radioimmunoassay method using antibody M1230 from a commercially available kit (Novo Research Institute, Bagsvaerd, Copenhagen, Denmark).[6] The assay was done after precipitation of proinsulin/insulin antibody complexes using polyethylene glycol.[7] The limit of detection was 0·025 nmol/l. The interassay coefficient of variation was less than 12% at a concentration of 0·13 nmol/l. Total $HbA_1$ was measured by electroendosmosis (Corning Ltd, Halstead, Essex, England), the normal range in our laboratory being 5·5–8·7%.

Student's unpaired *t* test was used to assess the significance of differences in age, duration of diabetes, insulin dose (units/kg), percentage of the dose given in the morning, percentage of the dose given as short acting insulin and $HbA_1$ between the groups. Student's *t* test was used when we compared fasting glucose concentrations between the groups. For data on the 24 hour profile we used the analysis of variance, the determinants being group and time.

## Results

There were no significant differences between the groups regarding age, total daily insulin intake (U/kg), or details of insulin regimen (table). The duration of diabetes was significantly longer in group B by a mean of 3·2 years.

Fasting blood glucose concentrations were considerably raised in both groups and slightly higher in group A, but not significantly so. The mean (SEM) in group A was 17·5 (1·4) mmol/l and in group B 16·5 (1·9) mmol/l. The glucose concentration rose to a peak in the mid morning (fig 1) and then dropped, falling faster and further in group A patients The greatest difference between the groups was during

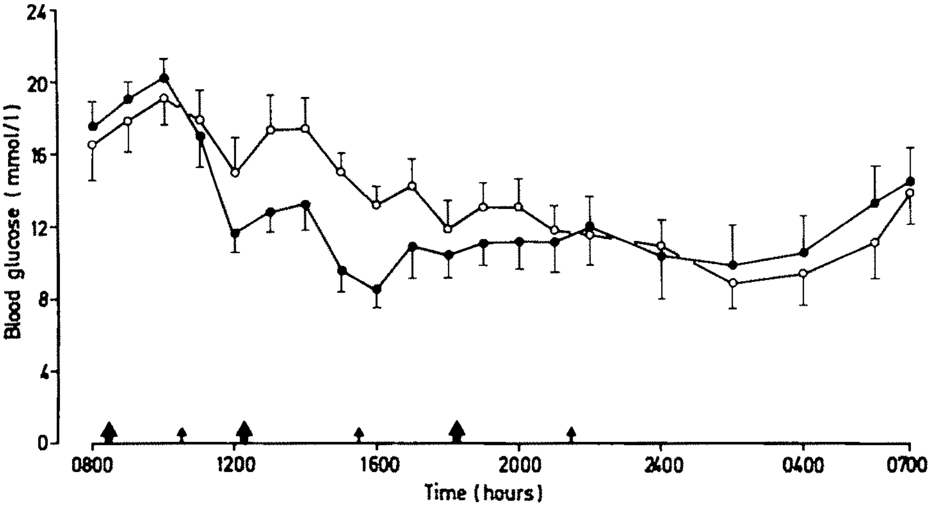

Fig 1 *Mean (SEM) 24 hour blood glucose profiles in 10 insulin dependent diabetic patients with (●——●) and without (○——○) appreciable circulating C peptide Meals (large arrows) snacks (small arrows).*

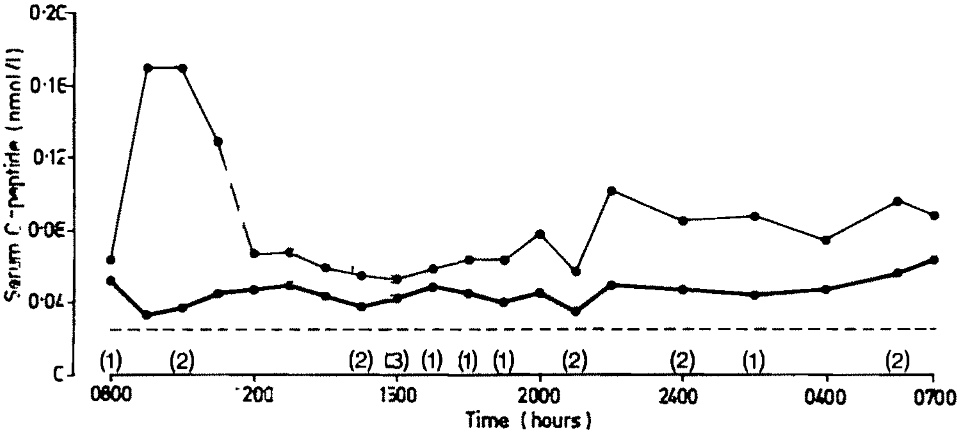

Fig 2 *24 hour C peptide concentration (median ●━━●), maximum ●——●) in 10 insulin dependent diabetic patients (group A) Lower limit of detection of assay – – –. No in parentheses refers No of patients with undetectable C peptide at specific times*

the afternoon; there was little difference during the evening and slightly higher concentrations in group A in the middle of the night. The average of the 24 hour mean (SEM) blood glucose profiles was 12·4 (1·2) mmol/l in group A and 13·4 (1·0) mmol/l in group B. Group A patients had a small but significantly lower mean blood glucose concentration ($F=3·94$, $p<0·05$). Fig 2 shows the maximum and median values of C peptide concentration in group A.

## Discussion

Residual insulin secretion may be assessed by the C peptide response to tolbutamide,[8] glucagon,[9] oral glucose,[10] or a standard meal.[9] The importance of residual insulin secretion, however, lies in the effect on blood glucose control during a normal day. We have considered our patients in two groups according to total 24 hour C peptide secretion, although endogenous insulin may be inhibited by low blood glucose concentrations or administration of exogenous insulin.[11] These effects were probably minimal in the group A patients as insulin secretion is maximally stimulated when blood glucose concentrations are greater than 12 mmol/l, and all patients had concentrations greater than this at some time during the 24 hours

The degree to which type 1 diabetics can secrete insulin after remission declines gradually with time and it is not surprising therefore that our patients with less C peptide secretion had had the disease longest,[12] although there was no difference in their ages.

Fasting blood glucose concentrations showed equally poor control in both groups at the start of the day. Clearly any help to control given by the small amount of endogenous insulin was of little value and this is a time of difficulty with control.[13–15] The small but significant effect on blood glucose concentration was most obvious in the afternoon. The mechanism of action of endogenous insulin is most likely to be on the liver as the small amounts detected are unlikely to raise peripheral insulin significantly, and hepatic production of glucose is more sensitive to insulin than peripheral glucose uptake.

This study shows that endogenous insulin secretion may exert metabolic effects even when present in low amounts. The effect is small and in clinical terms probably irrelevant. It is certainly less important than insulin dose, diet, and exercise. From an investigative viewpoint studies of control should take account of even small amounts of endogenous insulin secretion.

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# T cell response to anti-CD3 antibody in Down's syndrome

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SUMMARY The non-specific mitogen phytohaemagglutinin (PHA) and an anti-CD3 (OKT3) monoclonal antibody were used to measure the lymphocyte proliferative response in blood samples from 15 subjects with Down's syndrome. Blood from 15 healthy controls closely matched for age and sex was also assayed. The mean blastogenic value in PHA stimulated patient lymphocyte cultures was similar to that calculated in the controls. In contrast, the mitogenic response of lymphocytes from patients with Down's syndrome to anti-CD3 stimulation was on average significantly reduced. Immunofluorescence studies and additional experiments carried out by using semiallogeneic (maternal) monocytes as a source of antigen presenting cells showed that the impaired anti-CD3 induced mitogenesis in Down's syndrome could not be ascribed either to a lack of binding of the antibody to the trisomic cells, or to a defective monocyte-T cell interaction. These findings help to explain the cellular basis of the immune defect in Down's syndrome.

It has been suggested that an intrinsic T cell immune defect in Down's syndrome (trisomy 21) is responsible for the increased susceptibility to infections, malignant diseases, and autoimmune phenomena.[1] Studies of the Down's syndrome lymphocyte proliferative responses to specific and non-specific mitogenic agents, however, have produced conflicting data showing both normal and depressed responses. Data concerning the numbers of circulating trisomic lymphocytes and their immunoregulatory T cell subsets have been more controversial, with results varying from laboratory to laboratory.[2]

In the early 1980s the mitogenic effect of mouse monoclonal antibodies directed against one surface differentiation antigen—the CD3 antigen complex—was described[3] and the crucial role of CD3 antigen in T lymphocyte activation reported.[4 5] The present investigation was designed to measure the mitogenic action of an anti-CD3 monoclonal antibody on lymphocytes from patients with Down's syndrome. The response to anti-CD3 antibody was then compared with the reactivity of the trisomic cells against the polyclonal T cell activator phytohaemagglutinin (PHA).

## Patients and methods

Fifteen patients with Down's syndrome (trisomy 21) (nine boys and six girls) who were living at home, and 15 karyotypically normal age and sex matched healthy controls were studied. The age range in both groups was 1–30 years; seven subjects were less than 5 years old, four between 6 and 10, and four between 11 and 30. All were free of infection at the time of the study, and no patient or control subject was taking drugs known to affect the immune system.

Peripheral blood mononuclear cells were isolated by Ficoll-Hypaque (Lymphoprep, Nyegaard, Oslo, Norway) density gradient centrifugation, washed three times in Hanks's balanced salt solution and adjusted to a final concentration of $1\times10^6$ cells/ml in complete culture medium—that is, RMPI 1640 supplemented with antibiotics (penicillin 100 U/ml; streptomycin 100 µg/ml, L-glutamine (2 mM) and 10% heat inactivated fetal calf serum (all from Flow Laboratories, Irvine, Scotland).

Peripheral blood mononuclear cells ($1\times10^5$) were cultured in plastic, 96 well round bottomed culture plates (Nunc, Denmark) at 37°C in a humidified atmosphere containing 5% carbon dioxide in air. PHA-M (Gibco, Grand Island, New York, USA) and an anti-CD3 monoclonal antibody (IgG2a) (OKT3, Ortho, Raritan, New Jersey, USA) directed against a membrane antigen present on most human peripheral T cells as well as on a small proportion of thymocytes[6] were used as mitogens. The optimal blastogenic doses of both these reagents were established in preliminary experiments and found to be 1% for PHA and 25 ng/ml for anti-CD3 antibody. Cultures without PHA or anti-CD3 were used as controls. All cultures were performed in triplicate, and the cells pulsed with 0·5 μ CI ($^3$H) thymidine (specific activity 25 CI/mmol: The Radiochemical Centre, Amersham, England) after three days of incubation. Twelve hours later incorporation into DNA was measured using a liquid scintillation spectrometer.

An indirect immunofluorescence staining method incorporating fluorescein conjugated goat anti-mouse IgG (Meloy, Springfield, Virginia, USA) as a second labelling antibody[7] was used to calculate the proportions of CD3 antigen carrying cells in both Down's syndrome and control peripheral blood mononuclear cell preparations.

In the reconstitution experiments, Down's syndrome T lymphocytes (E rosette forming cells[8]) ($7\times10^5$/ml) were cultured in quadruplicate with plastic adherent semiallogeneic (maternal) monocytes ($3\times10^5$/ml) in complete medium alone or combined with anti-CD3 antibodies. The incorporation of tritiated thymidine in reciprocal experimental conditions was also assessed. To exclude the proliferation of residual heterologous T cells the cocultured monocyte suspensions were preincubated in medium containing 25 μg/ml mitomycin C (Kyowa Hakko, Kogyo, Tokyo, Japan) for 30 minutes at 37°C. Phorbol myristate acetate (PMA) (Sigma, St Louis, Missouri, USA) was also used at a concentration of 2, 5, and 10 ng/ml.

Statistical analysis was by Student's two tailed *t* test and probabilities of less than 0·05 were accepted as significant.

## Results

Although peripheral blood mononuclear cells from three post pubertal subjects with Down's syndrome responded poorly to PHA, the overall mean blastogenic response in our experimental group with Down's syndrome did not differ significantly from that calculated in the PHA stimulated control lymphocyte cultures. In contrast, there was a significant difference between the decreased proliferation induced by anti-CD3 in Down's syndrome and the normal mitogenic value (table 1). It can be seen, however, that a more pronounced defect in cultures with added tritiated thymidine after anti-CD3 stimulus was detected in two patients with Down's syndrome who responded poorly to PHA.

In four experiments a number of cells were available in which to analyse the kinetics of blastogenesis induced by anti-CD3. The kinetic pattern (seven days of incubation) in Down's syndrome was similar to that of the control lymphocyte cultures, both the cell populations showing a peak response on day 3. Then thymidine incorporation values gradually decreased to reach the starting cpm on day 6 (unpublished data). These findings suggest that anti-CD3 hyporesponsiveness in trisomy 21 is not attributable to the culture conditions.

Table 1 *Lymphocyte proliferative responses to phytohaemoagglutinin (PHA) and anti-CD3 monoclonal antibody in patients with Down's syndrome*

| *Case No* | *Sex* | *Age (years)* | *Net counts/minute (cpm)** | |
|---|---|---|---|---|
| | | | *PHA* | *Anti-CD3* |
| 1 | F | 1 | 83 917† | 22 101 |
| 2 | M | 1 | 86 440 | 29 848 |
| 3 | M | 3 | 114 913 | 18 013 |
| 4 | M | 3 | 96 913 | 33 415 |
| 5 | M | 3 | 100 021 | 44 984 |
| 6 | M | 4 | 73 696 | 16 929 |
| 7 | M | 4 | 124 419 | 39 821 |
| 8 | F | 7 | 119 887 | 31 717 |
| 9 | F | 8 | 77 633 | 19 411 |
| 10 | M | 8 | 94 824 | 16 584 |
| 11 | M | 10 | 119 800 | 24 624 |
| 12 | F | 16 | 63 494 | 10 424 |
| 13 | F | 18 | 51 601 | 23 983 |
| 14 | F | 23 | 66 487 | 13 817 |
| 15 | M | 30 | 101 720 | 38 746 |
| Mean (SEM)—patients: | | | 91 717 (5793) | 25 627 (2676)‡ |
| Mean (SEM)—controls | | | 95 634 (4147) | 37 063 (2244) |

*Cpm in mitogen stimulated lymphocyte cultures minus background cpm (cpm in unstimulated cultures), †mean of triplicate cultures, ‡$p<0·002$ (Student's *t* test for unpaired data)

Immunofluorescence studies were carried out to determine the proportions of CD3 bearing cells in both Down's syndrome and control preparations of peripheral blood mononuclear cells. Phenotypic analysis did not show numerical abnormalities in Down's syndrome: the mean (SD) percentage of anti-CD3 reactive trisomic lymphocytes was 66·5 (5·8), similar to the mean number of control fluorescent cells of 65·4 (5·6).

Mitogenesis induced by anti-CD3 depends on monocytes acting as auxiliary cells.[9] Reconstitution experiments with heterologous semiallogeneic monocytes were therefore performed to assess the functional integrity of the Down's syndrome macrophage/T cell association. Table 2 shows the results of a representative experiment. Irrespective of the origin of the monocytes, T cells responded to anti-CD3 stimulation according to the reactivity pattern of the unfractionated cells. This observation has been confirmed in two additional experiments.

Table 3 *Role of monocytes on anti-CD3 monoclonal antibody induced mitogenesis in Down's syndrome (DS)*

| *Donor cells* | *Counts/minute** *Mean† (range)* |
|---|---|
| Unfractionated (DS) | 14 580 (13 020–15 317) |
| T cells (DS)+monocytes (DS) | 12 407 (10 917–13 618) |
| T cells (DS)+monocytes (mother) | 15 938 (13 827–18 614) |
| Unfractionated (mother) | 39 309 (36 777–41 720) |
| T cells (mother)+monocytes (mother) | 33 519 (29 628–36 883) |
| T cells (mother)+monocytes (DS) | 40 444 (39 814–44 624) |

*Results corrected for incorporation of thymidine in the absence of monoclonal antibodies to minimise allogeneic helper effects, †quadruplicate cultures

## Discussion

Good experimental evidence suggests that the Down's syndrome lymphocyte proliferative response to PHA mitogen stimulation, which is normal during the first 10 years of life, declines rapidly and irreversibly thereafter.[10 11] In the present investigation Down's syndrome and control peripheral blood mononuclear cells displayed comparable levels of reactivity to PHA. Values for individual subjects with Down's syndrome varied widely however, and in three older patients were below the normal range. In contrast, a definite defect in trisomy 21 was seen when the effects of anti-CD3 antibody on the proliferation of resting peripheral blood lymphocytes were assayed. This defect, more pronounced in two postpubertal subjects, was also clearly evident in four children under the age of 10, suggesting that anti-CD3 hyporesponsiveness in Down's syndrome does not depend on age.

The mechanisms concerned in depressed mitogenesis are at present not clear. The lower reactivity to anti-CD3 could not be explained by the absence or paucity of CD3 antigens on the membrane surface of the trisomic cells as the proportion of CD3 bearing lymphocytes in Down's syndrome was similar to that calculated for the control group. T cell subset distribution was not investigated in our trisomic subjects. Conflicting results were reported in Down's syndrome when conventional monoclonal antibodies were used to discriminate helper/inducer (anti-CD4$^+$) from suppressor/cytotoxic (anti-CD8$^+$) T lymphocytes.[2 12–15] In addition, these results were often complicated by the fact that the sum of the percentages of cells stained for anti-CD4 and anti-CD8 antibodies exceeded the relative number of anti-CD3 staining cells.[14 15] A more complete panel of monoclonal reagents together with two-colour immunofluorescence techniques is needed so that the phenotype of mononuclear cell subpopulations with different functional activities can be identified microscopically. By means of these sensitive methods, overexpanded populations of suppressor (anti-CD8$^+$, anti-CD11$^+$)[2] and natural killer (anti-CD8$^+$, Leu7$^+$)[15] cells have recently been found in the blood of trisomic patients. Both these cells have granular lymphocyte morphology,[1 16] and presumably perform similar immunoregulatory cell functions.[16 17] Thus the defective proliferation induced by anti-CD3 and seen by us in trisomy 21 may in part be due to the increased number of cells which inhibit the immune response. Inhibitory mechanisms may also explain other Down's syndrome immunological abnormalities such as the depressed serum titres of 'natural' antibodies[18 19] and the impaired in vitro specific IgG production in response to recall antigens.[2]

By culturing lymphocytes from subjects with Down's syndrome with their own mother monocytes, and vice versa, we have shown that an intrinsic T cell immune defect—rather than a deficient helper macrophage function—affected anti-CD3 hyporesponsiveness in patients with Down's syndrome. This was further supported by the detection of an unchanged or decreased proliferative response induced by anti-CD3 in Down's syndrome lymphocyte cultures supplemented with PMA (unpublished data), a substance known to bypass the mechanisms by which accessory cells contribute to T cell growth initiated by anti-CD3 antibody.[20]

Blastogenesis induced by anti-CD3 is crucially dependent on the production and processing of the lymphokine interleukin 2.[21] In our laboratories we are evaluating interleukin 2 production and interleukin 2 receptor expression in anti-CD3 pulsed Down's syndrome lymphocyte cultures. Whatever the underlying cellular or molecular defects, or both, our results will provide further evidence that T cell derangement is an integral feature of Down's syndrome.

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# Personal health records: an evaluation

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SUMMARY A cohort of mothers whose babies were born over one calendar month were followed up eight to 11 months after being given a personal health record for their newborn babies. Eight per cent of mothers lost the records and three more said they had not been given a record while in hospital; a total of 10% of mothers had either lost or misplaced the record. There were no particular demographic characteristics which identified the mothers who were more likely to lose the record. Most parents liked personal health records and used them frequently, as did the community health staff. Most private doctors, however, did not find them useful. Before wider distribution of such records is contemplated health workers should be adequately prepared, especially doctors in the private sector.

The concept of patients having more control over the decisions that affect their health is becoming more popular. One step along the path of sharing information is the use of a personal health record (PHR) that contains information about a person's contacts with health workers concerning major health problems and treatment. Such records are already in use in South Australia where since 1981 they have been given to the mothers of all newborn children (CO Auricht, personal communication). They are also used in New Zealand, France, and in some African countries.[1] The records may be used by patients or their parents to review written information to consolidate the advice given at a consultation. They also provide a record, kept by the patient, which can then be used when patients change address and which identifies their general practitioners. The records may also contain relevant information about health education.[2 3]

There are few reports about the reactions of patients to PHR or whether they keep and use the records. To establish if such records would be useful to patients and professionals in New South Wales we evaluated the effect of introducing records for all newborn children at Camden Hospital in south western Sydney. This hospital was chosen because it had a maternity unit which served a population that was largely urban but had some semirural communities in this sense it differed from the remainder of Sydney which is totally urban.

This study is similar to one carried out in South Australia in 1976, but we sought additional demographic details of the parents who did not retain the record for their child to see if there was a particular group who would be less likely to use or keep the record.[4] Because it was felt that the record would be most useful for the mobile members of the population we also recorded demographic details of those who had left the address given at the initial interview. The reaction of health workers in the hospital catchment area was also sought.

For the purposes of this article we have described the Australian health system as being made up of broadly defined public and private sectors. The former is based in government funded institutions (public hospitals and community health centres). The private sector comprises self employed general practitioners, specialists, and a growing number of private hospitals.

The existing record system in the public sector is the traditional one of professional notes being made by nurses and doctors with the actual record kept in offices or a central records department. In the community health system records on young children (aged less than 5 years) would normally be stored until the child had been at school for one year and then destroyed. The record system used by the private sector varies from doctor to doctor.

## Subjects and methods

A PHR was developed based on the one already in use in South Australia. It was divided into patient and professional sections, and designed particularly for children aged 0 to 5 years. It included information about health education—immunisation; milestones of normal child development—vision and hearing questionnaires for parents; accident prevention advice, and information about normal growth including percentile charts. Pages for professional use included personal information (name, address, telephone number); birth data; growth graphs (length and height, weight, and head circumference); immunisation record; school health screening record; local doctors' and clinic nurses' names, addresses, and telephone numbers, progress notes for everyday problems, and a health problem summary sheet for important illnesses and allergies. Various colours were used to distinguish the sections. The pages, A5 in size, were bound in a folding plastic wallet.

A PHR was given at the time of discharge from the maternity unit (usually five days after delivery) to all mothers of babies born after 1 February 1985 at Camden Hospital. A cohort of mothers whose babies were born in one calendar month (June 1985) were interviewed and demographic details noted. These included age, education, marital status, number of children other than the index case, ethnic group, occupation of major breadwinner in the family, and combined family income. Certain babies were excluded from the study (stillbirths, babies who died in the neonatal period, babies who were to be adopted, babies who were transferred for intensive care, and babies of mothers who refused to accept the PHR). There were 180 births during the month of the study. Of these, one child was transferred to a referral hospital for intensive care; there were three stillbirths and one baby was adopted. Four mothers did not receive the PHR, all having been discharged within 48 hours of delivery. Four mothers refused to take the record home with them. Of the four, two mothers stated they would not use the PHR and two gave no reason for their decision. This left a sample population of 167

Eight to 11 months after the child was born an attempt was made to interview all 167 mothers at their homes. At that stage they were contacted by a second research assistant who was unknown to them. The mothers were asked if they had been given a PHR, when they were meant to use the record, whether they had read various parts of the booklet, and whether they were satisfied with the time when they received the PHR. We gauged how useful they found the PHR by asking three questions: what were the advantages and disadvantages in the record; what changes they would like to see if any; and if they would like a similar record for any of their other children.

We then posted a questionnaire to all health workers in the private and public sectors in the three local government areas served by Camden Hospital.

All the health workers had been contacted by mail during the six weeks before the introduction of the record. At that stage they were supplied with a copy of the record as well as two posters advertising and promoting its use, and an explanatory letter The second questionnaire was sent to 151 health workers including 123 doctors, 21 generalist community nurses, six clinic nurses, and one medical officer in child health who was included in the community health team. The second mailing was done 15 months after the introduction of the record. In the questionnaire they were asked, in three slightly different ways, if they were aware that the PHR was to be introduced. Firstly, they were asked if they had seen a PHR; secondly, if they had received a copy of the PHR plus the advertising posters through the mail; and thirdly, if they were aware that the record was going to be introduced locally. They were also asked to indicate how many patients or clients had brought the PHR with them at various contacts and whether they (the health workers) had read any of the information. Their opinion about how helpful it was, what advantages and disadvantages it had, and what changes they would suggest was also requested. They were also asked to identify the professional group to which they belonged

During the trial community health workers were asked to keep dual records—that is, to complete the usual entry in their own professional records plus the appropriate part or parts of the PHR. No directions were given to doctors in the private sector except that they were encouraged to complete the PHR.

## Results

### SURVEY OF THE PARENTS

Twenty mothers had left the address which was given at the time of the original interview. Of the 147 mothers who were able to be contacted, 12 mothers could not produce the record when they were seen, and three said that they had not received a record at the hospital, making a total of 10% of all the mothers contacted. There were no significant differences in maternal age, maternal education, marital status, number of children, ethnic group, occupational prestige, or combined family income between the mothers who still had the PHR and those who had lost or misplaced it.

When the progress notes and the number of contacts with health workers were studied, four of the 135 records had no entries. Seventy five per cent, however, had nine or more entries with separate dates.

Ninety one per cent of the records had progress notes made by the local clinic nurse but only 18·5% of the records had notes made by a doctor. Twenty eight per cent of parents had written in the progress

Table *Reactions of professionals to PHR*

| | *PHR helpful* | *PHR not helpful* |
|---|---|---|
| General practitioners | 15 | 6 |
| Specialists | 8 | 4 |
| Community nurses | 26 | 1 |
| Child health medical officers | 1 | 0 |

notes themselves Eighty seven per cent of parents said that they would like records for any future children and 37% of parents said that they would like records for siblings of the index child. Ten per cent of parents said they would not like similar records for other children.

Ninety two per cent of the mothers said they liked the wallet. A similar percentage of parents indicated that the index child had received the required number of immunisations. When this was cross tabulated with the actual record that had been made of immunisation it was found that an accurate record had been kept in 75% of cases. Ninety per cent of mothers said they were satisfied with the time that they were given the wallet (just after the birth of the child). Interestingly, over 80% of the mothers were prepared to pay for the wallet, and 52% said that they would pay between A$1·00 to A$3·00 for it.

Those who had moved away from their original addresses tended to be younger mothers (mean age 23·3) than those who were still at the address given at the time of first interview (mean age 27·0). This was significant ($p<0·01$). Those who left were also less likely to be married or in a stable relationship ($p<0·05$).

SURVEY OF THE PROFESSIONALS

Ninety (60%) of the questionnaires were returned. Eight doctors and one community nurse had left the addresses they had previously given. The 54 doctors comprised 36 general practitioners and 18 specialists. Thirty one general practitioners and 12 specialists (80% of the doctors) said they had seen the PHR and all of the community health staff said that they had done so. The same 31 general practitioners but only seven specialists (70% of the doctors), had made at least one entry in the PHR. All but one of the community nurses had recorded comments, but the one dissenter had only just started work in the area. Thus a total of 80% of the surveyed local health staff had completed at least one entry in a PHR.

In response to how helpful they found the PHR, 24 (44%) doctors—16 general practitioners and eight specialists—found it moderately or very helpful. The eight specialists comprised three obstetricians, three paediatricians, one surgeon and one other. Ten (19%) doctors (six general practitioners and four specialists) found it no help at all. The specialists (three dermatologists and one psychiatrist) admitted to seeing no children professionally. Ninety three per cent of the community health staff found it moderately or very helpful. The reasons for the PHR not being helpful were sought but only five doctors responded; all five said that they felt that it was too time consuming

## Discussion

This survey resulted in three major findings. Firstly, most parents liked the idea of the PHR for their children. Ninety per cent had retained the PHR and 136 of 140 records had entries made in the progress notes, 75% of which had nine or more entries. In addition, 87% of those studied would use similar records for future children. Thus parents are likely to keep a PHR and use it frequently. In this respect our findings are similar to those of the South Australian study in which 88% of the mothers still had the record in their possession one year after it was introduced. The second major finding was that no particular socioeconomic group was more likely than any other to lose a PHR. It is impossible in the context of the study to know whether a PHR was retained or what use was made of it by the 20 mothers who had left their original addresses.

The other major finding was that professional acceptance contrasted sharply between the public and private sectors. In the former (community nurses and one medical officer) 93% found the record useful. Only 44% of the private sector, however, found the record to be helpful. This compared with 58% of the 40 doctors who took part in the South Australian trial. While this needed to be taken in the context of those who tended to see children more frequently (for example, paediatricians and general practitioners) and who therefore tended to accept the PHR more readily than those whose paediatric workload was less, it highlighted a major obstruction to the success of such a programme. We postulate that the apparent reluctance of the private sector doctors to fill out a PHR is because they fail to see any benefit for themselves or their patients.

We feel that the PHR encourages parents to be key members of the 'team' offering primary health care to children. Their actions in dealing with most childhood illnesses are to be encouraged and facilitated with accurate, easily understood health education advice such as that available in a PHR.[5]

Though it was not possible to examine the impact of such material during this study, the PHR included 'professional' sheets which would effectively replace other documents in present use in the community health system, for instance the infants' health records, the immunisation records and the school health screening cards. We feel that the drawing together of such information would enhance the passing on of a child's health information and help to solve the storage problems which plague most medical records departments.

Our conclusion was that the record was well accepted by patients. It was used well by the public sector health workers but not by private sector doctors. We recommend that before wider distribution of a PHR takes place the various medical colleges and organisations should be consulted and their support sought The campaign should be preceded by general advertising in the community but the results of both our study and that in South Australia indicate that with little preparation there is still likely to be wide acceptance of such a policy; most of the preparatory efforts must therefore be directed at the private health sector

Finally, though the record that we used was not quite the same as that presently in use throughout South Australia, it would make good sense to have as universal a record as possible throughout Australia. Though trials up to now have been aimed at children, the major thrust of such an idea is for patients to use the PHR throughout their lives. This is already occurring in some general practices and is outlined in a positive report by Gawthorn, who described a PHR used especially in the elderly patients.[2]

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# Clinical predictors of outcome in encephalitis

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SUMMARY Twenty five patients with encephalitis were studied prospectively, and their clinical and virological features compared with outcome. Among 22 patients with laboratory confirmation of virus infection, evidence of direct effect on the central nervous system by the virus occurred significantly more often both in those with a monophasic illness compared with those with a biphasic illness, and in those with focal neurological signs localising in the cerebral hemispheres compared with those without such signs. Young age at presentation, low score on the Glasgow coma scale, disruption of oculocephalic responses, and laboratory evidence of virus infection within the central nervous system were significantly associated with poor outcome. Computed tomography results, concentrations of creatine phosphokinase BB isoenzyme in cerebrospinal fluid, and procoagulant activity in cerebrospinal fluid were not predictive of outome.

Acute encephalopathies of viral or unknown cause occur most commonly in the first decade of life with a peak incidence of 1–2/1000 in the first six months of life. These illnesses are an important cause of handicap in the community: of those affected under the age of 3 years, 17% die and 42% are left with moderate to severe handicap (unpublished data from the British National Childhood Encephalopathy Study, 1981). Viral encephalitis is the usual clinical diagnosis but histological confirmation is rarely obtained. An association with virus infection has been shown in only 20–40% of series of consecutive patients with this diagnosis,[1–4] unless the patients were highly selected.[5] Because such series may have included a large number of non-viral encephalopathies, definition of the associations among aetiology, clinical features, and outcome have been largely restricted to small subgroups in which a specific virus has been implicated clinically[6–8] or histologically.[9 10] Study of the clinical features might be helpful not only in distinguishing viral from post-viral encephalitis,[3] but also in establishing a provisional prognosis, because in many patients a specific virus is never identified.

We prospectively studied 32 patients with acute encephalopathies in whom initial investigation seemed to exclude a non-viral cause. An association with virus infection was shown in most of them[11] and extensive immunological investigation showed no evidence of immune deficiency.[12] We analysed the clinical features of 25 patients with a clinical diagnosis of encephalitis according to their prodromal illness, their neurological signs, and the site of the virus infection.

## Patients and methods

Twenty nine children (18 boys and 11 girls) aged 0·2 to 13 years (median 3·8 years; quartiles 1·3 and 6·5 years) and three adults aged 22 to 38 years were studied prospectively because (a) they had either acute depression of conscious level or acute onset of focal neurological signs that had not been precipitated by a seizure and (b) no non-infectious or bacterial causes were found on initial investigation. Thus patients with either suspected viral encephalitis or unexplained encephalopathy were studied. Patients with nuchal rigidity but without focal neurological signs or obvious decrease in conscious level (suggesting uncomplicated viral meningitis) did not fulfil the criteria for admission. The patients were drawn from the following sources: paediatric neurology (n=15); paediatric infectious diseases (n=7); general paediatrics (n=7); and adult medicine (n=3). Seventeen were referred to a specialised centre from the hospital to which they were first admitted.

The history was taken and repeated neurological examinations performed and recorded on a standardised form by one of us (CRK). The examination was repeated at least daily for the first four days in hospital and at least weekly thereafter until discharge. Conscious level was assessed using the Glasgow coma scale as modified for children.[13] Questionnaires about the childs' behaviour before the illness were completed by parents and teachers when the child was entered in the study. The management of seizures and raised intracranial pressure, and the indications for the use of acyclovir were standardised. Clinical circumstances led to deviation from this policy in only one patient (case 27).

Full blood counts, examination of the cerebrospinal fluid and biochemical analysis of the serum were done by the hospital laboratory services The virological methods used and criteria for defining active virus infection have been reported elsewhere.[11] EEG and computed tomography of the brain were classified according to the consultant's written report The BB isoenzyme of creatine phosphokinase (CPK–BB) was measured in cerebrospinal fluid by Dr RJ Thompson, Cambridge, England. The ratio of the activated and non-activated derivatives of plasma clotting factor VII (VIIc:VIIt ratio), an indirect measure of thromboplastin activity, was measured in cerebrospinal fluid and plasma by the coagulation laboratory at the Clinical Research Centre, Northwick Park.

Outcome was evaluated by one of us (CRK) seven to eight months after the patient's discharge from hospital using neurological examination and, for children under the age of 8 years, the Griffiths mental development scales In addition, children over the age of 5 years were tested by an experienced clinical psychologist (RS) using the revised version of the Weschler intelligence scales for children (WISC–R). Behaviour was assessed in children aged 18 months to 5 years using the Richman behaviour checklist,[14] and in the children over the age of 5 using the Rutter A and B scale questionnaires for parents and teachers, respectively.[15] Outcome was assessed in all surviving patients except for one boy (case 20) whose mother did not wish to have him evaluated further. He seemed to have made a full and rapid recovery and was placed in outcome category 5 in the analysis.

Outcome was expressed in five categories ranked from 1 to 5 constructed from three variables: neurological examination, developmental quotient, and behaviour. Categories were assigned as follows: 1=dead or development quotient <40; 2=development quotient 40–80 plus major neurological signs or behaviour problem; 3=development quotient 40–80 without major neurological signs or behaviour problem; 4=development quotient >80 plus major neurological signs or behaviour problem, and 5=development quotient >80 without major neurological signs or behaviour problem.

Major neurological problems were defined as those that interfered with function to the extent that the patient required assistance with activities of daily living. A behaviour problem was defined as a problem perceived by the parent or teacher, together with a rise in score in the behaviour questionnaire by more than five points over that before the illness to a value on the Richman or Rutter scale showing an established association with behavioural problems.

The outcome thus expressed was compared with clinical and laboratory variables measured at the time of the neurological illness. Acute phase variables were compared with category of outcome by regression analysis on continuous effects, and analysis of variance on factorial effects. Although this entailed the treatment of categories of outcome as continuous, we preferred it to a $\chi^2$ analysis as the marginal totals were too small for such an analysis to be valid. Furthermore, the necessary assumption of a normally distributed residual variation was supported by a p value of 0·68 in a Shapiro and Wilk W test for non-normality performed on the residuals Tests for the significance of associations between acute phase variables and category of outcome were done using the F test. A two tailed Fisher's exact test was used to assess the significance of all other differences.

## Results

### DURATION OF SYMPTOMS AND DIAGNOSIS

The median delay between the onset of any symptom and entry into the study was nine days (quartiles five and 15 days) Half the patients were entered within three days of the onset of neurological symptoms or signs (quartiles two and five days). One patient (case 26) was exceptional in having a neurological illness for 30 days prior to entry. There was no significant difference between the duration of preceding symptoms in patients with monophasic illnesses compared with those with biphasic illnesses.

From the history, clinical examination, biochemical and neuroradiological investigations, but without the results of virological investigations, patients were placed in the following diagnostic categories: encephalitis (n=25); haemorrhagic shock and encephalopathy (n=2)[16]; Reye's syndrome (n=1); cerebrovascular accident with respiratory infection, (n=1); and non-infectious cause (n=3) (moyamoya disease n=1, haemangioma at the craniocervical junction n=1, intracerebral haemorrhage n=1) All results reported below refer exclusively to the 25 patients with encephalitis.

The diagnosis of encephalitis was made on clinical rather than histological grounds, but laboratory confirmation of virus infection either within the central nervous system (n=11) or outside the central nervous system (n=11) was subsequently obtained in all but three patients (table 1).[11] Of these three patients one (case 25) had a subacute illness the symptoms of which included a persistent high fever and a rash; the neurological prodrome of 30 days and hospital stay of three months were unusually prolonged. The case histories of the other two patients (cases 27 and 28) were also suggestive of infection. Delay in presentation was consistently associated with lower yields from virological investigation in this study[11] and seemed the most likely explanation for our failure to identify the causal agent in these two patients who presented after 10 and 11 days of symptoms, respectively. We have therefore considered these three patients together with the other patients with a clinical diagnosis of encephalitis in subsequent analyses.

## CLINICAL AND LABORATORY FEATURES OF PATIENTS WITH ENCEPHALITIS

Details of symptoms, clinical examination, neuroradiological investigation, the infective agent, and the outcome are given individually for each patient in tables 2 and 3.

Eighteen patients had a prodromal illness that was not neurological (respiratory in nine, respiratory and gastrointestinal in one, rash in six, myalgia in one, and fever alone in one). The remaining seven patients had exclusively neurological symptoms. Clear signs of recovery from the prodromal illness before the onset of the neurological illness (a biphasic illness) were seen in 12 patients, although only four had an interval of entirely normal health between the two illnesses. Among the 22 patients with laboratory confirmation of virus infection, a significantly larger number of those with a monophasic illness had laboratory evidence of virus infection within the central nervous system than of those with a biphasic illness (eight of 10 and three of 12; $p<0{\cdot}03$).

Focal neurological signs were seen in 20 (80%). These were divided into three categories: cranial nerve signs, ataxia, and the combination of rigidity, spasticity, tremor or weakness of a distribution which suggested that the brain rostral to the brain stem and cerebellum was affected—'hemispheric signs'. Among the 22 patients with laboratory confirmation of virus infection, those with hemispheric signs were significantly more likely to have laboratory evidence of virus infection within the central nervous system than those without such signs (nine of 12 and two of 10; $p<0{\cdot}03$).

Significant disturbance of consciousness (modi-

Table 1 *Laboratory evidence of infection in 25 patients with clinical diagnosis of encephalitis*

| *Site of infection and evidence* | *Infecting Virus* | *No of patients* |
|---|---|---|
| **Within the central nervous system:** | | |
| Serology positive* and interferon in cerebrospinal fluid | Herpes simplex | 2 |
| | Enterovirus | 2 |
| | Respiratory syncytial virus | 1 |
| | Measles | 1 |
| | Adenovirus | 1 |
| Serology positive and high specific IgG ratio† | Measles | 3 |
| | Respiratory syncytial virus | 1 |
| Serology positive and virus cultured from cerebrospinal fluid | Enterovirus | 1 |
| Interferon in cerebrospinal fluid only | Unidentified | 1 |
| One or more of above | | 11 |
| **Outside the central nervous system only:** | | |
| Virus cultured from respiratory tract and serology positive* | Enterovirus | 1 |
| | Respiratory syncytial virus | 1 |
| Serology positive* | Varicella | 3 |
| | Enterovirus | 2 |
| | Respiratory syncytial virus | 2 |
| | Measles | 1 |
| | Mycoplasma | 1 |
| Interferon in serum | Unidentified | 1 |
| One or more of above | | 11 |
| None identified | | 3 |

*Fourfold rise in IgG between paired sera, or high IgG and IgM concentrations in acute serum

†Specific IgG ratio = Specific cerebrospinal fluid × total serum IgG/Specific serum IgG × total cerebrospinal fluid IgG

fied Glasgow coma scale score of <14) was seen in eight of 12 (67%) of those with a biphasic illness and 11 of 13 (85%) of those with a monophasic illness. The score fell below 11 in 13 (52%) and below six in three (12%). Disruption of oculocephalic responses, normally induced by the application of cold water to the external auditory meatus, was seen in two patients. An increase in intracranial pressure was suspected clinically in five, and measured as >20 mm Hg in three patients including one infant

Table 2 *Clinical features and outcome in patients with encephalitis and laboratory evidence of virus infection of the central nervous system.*

| *Case No* | *Infecting virus* | *Age* | *Days of symptoms* | *Monophasic or biphasic illness* | *White cells in cerebrospinal fluid* | *High* albumin ratio* | *Admission coma scale score* | *Neurological examination* | *Follow up* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | *Neurological signs* | *Developmental quotient* |
| 1 | Echovirus | 6·5 | 4 | Monophasic | No | No | 12 | Hemispheric | Normal | 108 |
| 2 | Echovirus | 11·0 | 3 | Monophasic | Yes | No | 14 | Brain stem | Normal | 107 |
| 3 | Coxsackie | 0·8 | 11 | Biphasic | Yes | Yes | 9 | Non-focal | Died | Not done |
| 4 | Herpes simplex | 38 | 7 | Monophasic | Yes | Yes | 13 | Hemispheric | Normal | 119 |
| 5 | Herpes simplex | 1·6 | 6 | Monophasic | No | No | 6 | Hemispheric | Hemiplegia | 76 |
| 6 | Measles | 6·5 | 10 | Monophasic | Yes | Yes | 14 | Hemispheric | Normal | 78† |
| 7 | Measles | 3·8 | 18 | Monophasic | No | No | 11 | Hemispheric | Minor | 76 |
| 8 | Measles | 12·3 | 18 | Biphasic | No | Yes | 14 | Hemispheric | Minor | 68† |
| 9 | Respiratory syncytial virus | 13·0 | 4 | Monophasic | Yes | Yes | 11 | Hemispheric | Minor | 119 |
| 10 | Adenovirus | 1·3 | 7 | Monophasic | No | Yes | 7 | Hemispheric | Minor | 76 |
| 11 | (?)Influenza A | 3·0 | 10 | Biphasic | Yes | No | 10 | Hemispheric | Normal | 127 |

*CSF=serum ratio >3SD above reference mean, †=severe behaviour problem

Table 3 *Clinical features and outcome in patients with encephalitis either with virus infection outside central nervous system only (case Nos 12–22) or without laboratory confirmation of infection (case Nos 23–25)*

| *Case No* | *Infecting virus* | *Age* | *Days of symptoms* | *Monophasic or biphasic illness* | *White cells in cerebrospinal fluid* | *High* albumin ratio* | *Admission coma scale score* | *Neurological examination* | *Follow up* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | *Neurological signs* | *Developmental quotient* |
| 12 | Coxsackie | 5·5 | 30 | Biphasic | No | No | 14 | Hemispheric | Normal | 106 |
| 13 | Coxsackie | 38·3 | 33 | Biphasic | Yes | Not done | 13 | Minor | Minor | Not done |
| 14 | Coxsackie | 6·5 | 3 | Monophasic | No | No | 10 | Non-focal | Minor | 115 |
| 15 | Polio | 0·2 | 5 | Monophasic | Yes | Yes | 13 | Non-focal | Normal | 100 |
| 16 | Varicella zoster | 1·3 | 13 | Biphasic | No | Not done | 9 | Hemispheric | Normal | 108 |
| 17 | Varicella zoster | 4·5 | 7 | Biphasic | No | Not done | 13 | Ataxia | Normal | 110 |
| 18 | Varicella zoster | 4·5 | 7 | Biphasic | No | Not done | 14 | Ataxia | Normal | Not done |
| 19 | Measles | 5·0 | 8 | Biphasic | Yes | No | 11 | Non-focal | Normal | 117 |
| 20 | Respiratory syncytial virus | 1·0 | 14 | Biphasic | No | Not done | 14 | Ataxia | Normal | 98 |
| 21 | Respiratory syncytial virus | 3·0 | 31 | Biphasic | Yes | No | 13 | Brain-stem | Normal | 99 |
| 22 | Mycoplasma | 3·8 | 14 | Biphasic | No | No | 13 | Ataxia | Normal | 109 |
| 23 | Unknown | 22 | 30 | Monophasic | Yes | Yes | 7 | Hemispheric | Minor | Normal |
| 24 | Unknown | 0·6 | 11 | Monophasic | No | No | 3 | Hemispheric | Major | <40 |
| 25 | Unknown | 13 | 10 | Monophasic | Yes | Yes | 13 | Non-focal | Normal | 97† |

*=CSF serum ratio >3SD above reference mean, †=severe behaviour problem

without any specific clinical signs of raised intracranial pressure (case 24).

Transudation of protein into the cerebrospinal fluid was suggested by an albumin ratio of greater than three standard deviations above a reference mean for children and young adults in nine of the 20 patients who had albumin concentrations measured in both cerebrospinal fluid and serum. Albumin ratios were significantly higher in patients with infection of the central nervous system than in those with infection outside the central nervous system alone ($n_1=6$, $n_2=9$, $T_2=30$, $p<0\cdot05$, Wilcoxon two sample test).

The EEG was abnormally slow in 18 of 19 tested patients (highest frequency $>\theta$ in seven, $\theta$ in eight, and $<\theta$ in three). Abnormalities were seen on computed tomography in nine of 19 tested patients (focal low attenuation in six, diffuse low attenuation of white matter in two, and enlarging ventricles in one). Abnormalities were not always detectable on the first examination.

### OUTCOME AND ITS CORRELATION WITH CLINICAL FEATURES AT PRESENTATION

Outcome categories were assigned. The distribution of acute phase variables that were significantly associated with outcome are shown by category for all 25 patients with a clinical diagnosis of encephalitis in table 4. A poor outcome was associated with low scores on the modified Glasgow coma scale ($p<0\cdot05$), age of less than 3 years ($p<0\cdot02$ excluding adults whose inclusion increased the significance of the finding), abnormality of oculocephalic responses ($p<0\cdot001$), and laboratory evidence of virus infection within the central nervous system ($p<0\cdot02$). After correcting for coma scale score on admission, or for age, the other three factors remained significantly associated with outcome. If developmental quotient was used as a measure of outcome in survivors the same associations persisted, suggesting that the associations were not artefacts of the chosen system of categorising outcome.

Table 4 *Acute phase factors associated with outcome in 25 patients with a clinical diagnosis of encephalitis*

| *Acute phase factor* | *No of patients in outcome categories* | | | | | *p Value* |
|---|---|---|---|---|---|---|
| | *1* | *2* | *3* | *4* | *5* | |
| Age (excluding three adults). | | | | | | |
| <3 years | 2 | | 2 | 1 | 2 | 0·02 |
| >3 years | 0 | 3 | 0 | 1 | 11 | |
| Minimum modified Glasgow coma scale score | | | | | | |
| <5 | 1 | | 0 | 0 | 1 | |
| 5–9 | 1 | | 2 | 0 | 6 | 0 04 |
| 10–15 | 0 | | 0 | 2 | 9 | |
| Oculocephalic responses | | | | | | |
| Normal | 0 | 3 | 2 | 2 | 16 | 0 0004 |
| Abnormal | 2 | 0 | 0 | 0 | 0 | |
| Laboratory evidence of viral infection. | | | | | | |
| CNS | 1 | 3 | 2 | 0 | 5 | |
| non-CNS | 0 | 0 | 0 | 1 | 10 | 0 02* |
| none | 1 | 0 | 0 | 1 | 1 | |

*comparison between central nervous system and other two categories combined

Outcome seemed to be associated with only one of the immunological measurements at the time of the acute illness; if patients were divided into those who developed sequelae and those who did not, the cerebrospinal fluid:serum albumin concentration ratio was significantly higher in those with sequelae ($n_1=9$, $n_2=9$, $T_2=59\cdot5$, $p<0\cdot05$, Wilcoxon two sample test).

In addition, both low scores on the coma scale on admission and a greater degree of slowing on EEG were associated with poor outcome, although these were not statistically significant. Abnormalities on computed tomography were not associated with outcome, and there was no correlation between outcome and concentrations in the cerebrospinal fluid of either CPK–BB isoenzyme (13 patients), or the VIIc:VIIt ratio (19 patients), although cerebrospinal fluid was sampled from patients in all categories.

## Discussion

We have taken encephalitis caused by infection with any one of several common viruses to be a single entity for the purpose of analysing the prognostic value of certain clinical features. Although such an analysis ignores differences in pathogenesis associated with different viruses,[17] it has the advantage of being clinically applicable to the 60–80% of encephalitides in which a specific agent is not identified by routine virology.[1–4]

For the minority in which a virus can be identified, the prognoses associated with different agents are distinguishable but with rare exceptions (such as rabies, Lassa fever, and eastern equine encephalitis) similar to one another, mortality varies by less than 15% among encephalitis complicating infection with rubella (20%) or measles (9%–27%),[6 18] adenovirus 7a (14%),[19] and herpes simplex type 1 encephalitis treated with acyclovir (19%–31%).[9 10] The incidence of sequelae is 25–40% both in these encephalitides and in those with a lower mortality caused by enteroviruses in infancy,[20] mumps,[7] and chickenpox.[6 8] The prognosis of encephalitis after infancy caused by enteroviruses, influenza viruses A and B,[21 22] parainfluenza viruses 1, 2, and 3, and respiratory syncytial virus, is ill defined. Thus the prognosis of childhood encephalitides associated with common viruses may be determined more readily from the clinical features of the illness than from knowledge of the identity of the virus.

It is commonly thought that the virus either directly invades the brain or triggers an immunologically mediated illness one to two weeks after an infection which may not have affected the central nervous system directly. The presence of a particular virus does not mean that the neurological illness must be early or late; measles,[23] influenza,[21 22] varicella zoster,[6 24] and herpes simplex[25] may lead to either type of illness. In the present study enterovirus and respiratory syncytial virus infections were found both within the central nervous system and confined to sites other than the central nervous system, confirming that both types of encephalitis may be caused by the same agent. Furthermore, it is not clear how often both viral and immunologically mediated diseases may coexist, because most patients do not come to necropsy. We therefore feel that subdivision of encephalitis on clinical grounds is in theory as reasonable as subdivision by causal agent, and potentially as useful in practice.

Kennard and Swash[3] reported that mortality was lower (5% and 20%) but morbidity higher (42% and 22%) among patients with an interval of normal health between the first illness and the neurological illness than among those without such an interval. Two clinicovirological groupings emerge from the present study: the first consists of a monophasic illness with neurological signs of impairment of the cerebral hemispheres and laboratory evidence of direct involvement of the central nervous system by a viral infection, and the second of a biphasic illness without focal signs of impairment of the cerebral hemispheres, and with evidence of viral infection only at sites other than the central nervous system. In this series encephalitis was associated with mortality or morbidity in almost half the patients with viral infection of the central nervous system, but not in those with evidence of infection by the same viruses confined to sites other than the central nervous system at the time of their neurological illness

Focal neurological signs were associated with a poor prognosis in two earlier series if present[2] or 'marked',[3] but were not more precisely associated with virology or outcome. Both studies were retrospective and concerned mainly adult patients. In the present prospective study that was predominantly of children the presence of focal neurological signs was a marker for infection of the central nervous system and, therefore, of a higher probability of long term sequelae. This may also have been true for the earlier series.

In hypoxic or ischaemic encephalopathy the level of consciousness, length of coma, and presence of abnormalities of oculocephalic responses or of EEG may predict outcome.[26 27] Of these, conscious level and abnormal oculocephalic responses were also predictive of outcome in the present study A significant association between the severity of the EEG abnormality and outcome might have emerged if larger numbers had been studied, but the weakness of this association and the relative lack of predictive value of the length of coma may be a reflection of the fact that the symptoms are reversible when caused by a virus, but not when caused by hypoxia or ischaemia. The same association between conscious level and outcome has been reported in encephalitis caused by measles, varicella zoster, rubella,[6] and herpes simplex type I.[10] An association between seizures and poor outcome reported by other authors was not confirmed by our results.

An important finding in this study was that young age at presentation was related to poor outcome. Indeed, most of the morbidity was among the youngest patients with less than half (three of 7) of patients under the age of 2 years recovering uneventfully. An independent effect of age is suggested by its persistent association with outcome even after adjusting for either conscious level on admission or the presence of laboratory evidence of virus infection within the central nervous system.

The association between transudation of albumin into the cerebrospinal fluid and evidence of viral infection of the central nervous system is of interest. Our observations do not, however, enable us to determine whether this is a cause or a consequence of breakdown of the blood brain barrier.

This series did not confirm the association between pleocytosis and outcome, which has previously been reported.[2 3] Furthermore, in spite of earlier more encouraging reports on small mixed groups of patients with viral meningitis, bacterial meningitis, or encephalitis,[28 29] signs of neuronal damage, concentrations of CPK–BB isoenzyme, and the VIIc:VIIt ratio in the cerebrospinal fluid were neither sensitive nor specific in the present study. This may reflect either release from areas of the central nervous system where damage does not find clinical expression, or the unavoidable variation in the timing of sampling in relation to the onset of the illness. Computed tomography during the acute illness proved, unlike EEG, only moderately sensitive in the detection of encephalitis (as previously reported for herpes simplex encephalitis).[30] In addition the presence of abnormalities on computed tomography was not of predictive value; good and bad outcome was seen in patients with normal pictures, and in those with unilateral necrosis or diffuse low attenuation of white matter.

In conclusion a monophasic illness prior to hospital admission, and the presence of focal neurological signs suggesting disease of the cerebral hemispheres may indicate a greater likelihood of direct effect on the central nervous system by the virus in suspected viral or post-viral encephalitis in childhood. This in turn is associated with long term sequelae. With a uniform policy of management, the outcome of these illnesses seems to be predictable by the clinical features of presentation at a young age, low conscious level, abnormal oculocephalic responses, and laboratory evidence of direct effect on the central nervous system by the virus; all these exercise unfavourable effects. These factors should be taken into account in the evaluation of methods of treatment. Further studies are needed to establish the stability of these factors in a larger sample.

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## *Short reports*

# Endoscopic evacuation of an intracerebral and intraventricular haemorrhage

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SUMMARY An intracerebral and intraventricular haemorrhage associated with acute post-haemorrhagic ventricular dilatation was evacuated under endoscopic view in a 9 day old preterm infant. Ventricular dilatation was arrested, but a moderate left spastic hemiparesis remained. The physical and mental development of the baby was normal.

Intracerebral and intraventricular haemorrhage occurs in up to 43% of very low birthweight infants,[1] and their prognosis is poor because of acute brain damage and post-haemorrhagic hydrocephalus.[1-3] We were unable to find any previously published reports of endoscopic evacuation of an intracerebral and intraventricular haemorrhage in neonates.

## Case report

A boy weighing 1410 g was delivered by caesarean section at 30 weeks' gestation. The Apgar score was 4 at one minute and (after intubation) 8 at three minutes. Respiratory support was continued owing to wet lung. A routine echoencephalogram performed five hours after birth was normal and the baby was neurologically unremarkable. His condition deteriorated 43 hours later. While he was on continuous positive airway pressure he had repeated spells of severe apnoea with cyanosis and bradycardia, apathy, and hypotonia as well as loss of prompt responses to stimulation which he had shown before. At this time brain ultrasonography showed an extensive haemorrhage in the right frontoparietal region with displacement of the midline structure and blood in the lateral ventricles. Subsequent ultrasound examinations showed that the extent of the haemorrhage increased until the seventh day and that a rapid dilatation of the ventricles took place. The computed tomography (CT) scan findings on the eighth day are shown in fig 1a. The neurological state was unchanged There were no spontaneous movements and there were poor reactions to stimuli. Spontaneous breathing was infrequent and intermittent mandatory ventilation was therefore continued.

Because of the relatively stable neurological state and vital signs, we decided to evacuate the intracerebral blood. We anticipated the procedure might lead to a reduction in the intracranial pressure as well as arresting the ventricular dilatation. We assumed that the dilatation was at least partially caused by occlusion of the interventricular foramina

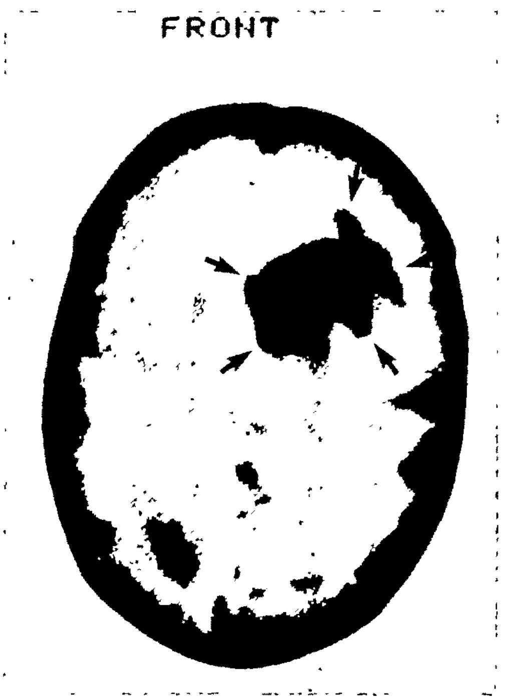

Fig 1a *Computed tomogram one day before surgery Blood clot is situated in right anterior horn and periventricular white matter (indicated by arrows)*

by blood clot. On the ninth day, after general anaesthesia, a right frontal trepanation (1 cm) was performed A neuroendoscope with a built-in neodymium YAG laser (Storz type 26162 B) with an external shaft of 6·0 mm in diameter was introduced under sonographic control. A large part of the parenchymal portion of the haemorrhage was removed using endoscopic channels for irrigation and suction. The ventricular system was then entered and inspected and blood clot was removed from the anterior horn and cella media of the right lateral ventricle as well as the right interventricular foramen.[4 5] Finally an external drain was placed into the right anterior horn which permitted continuous measurement of intracranial pressure and cerebrospinal fluid production.

Six hours after surgery the patient's neurological state had improved considerably. He had normal muscle tone, prompt responses to painful stimuli, symmetrical movements, and regular breathing, intermittent mandatory ventilation was therefore discontinued. Over the next six days intracranial pressure was no more than 8 mm Hg, and ventricular fluid secretion averaged 6 ml/day (both measured by the external drain). The computed tomogram taken on the seventh postoperative day (the drain having been removed a day before) is shown in fig 1b. Subsequently ultrasound imaging and transfontanelle measurements of the intracranial pressure (LADD M 1000) were carried out. We noticed a slight enlargement of the left ventricle and a transient rise of the intracranial pressure up to 15 mm Hg. Acetazolamide (50 mg/kg/day) was given from the 12th to the 40th postoperative day.

On the 46th postoperative day the baby was discharged home. Before this, ultrasound examination showed that the left ventricle was moderately enlarged (6 mm in width) and that there was a porencephalic cyst at the site of the original parenchymal haemorrhage communicating with the right ventricle (fig 2). Intracranial pressure was 6–8 mm Hg, and the occipitofrontal head circumference was growing along the 25th percentile. The baby had normal muscle tone, symmetrical posture as well as spontaneous movements, good sucking, and he was gaining weight. Eleven days before discharge we noticed a discrete peripheral paresis of the right facial nerve. We assumed that this was a congenital anomaly because there was also dysplasia of the ipsilateral auricle.

At 3 months of age he had general muscular hypertonia with opisthotonus, asymmetric tonic neck reflex and asymmetric posture of the spine; intensive physiotherapy was started At 5 months he was following moving objects, grasping only with the right hand, and crawl activity of the left leg was

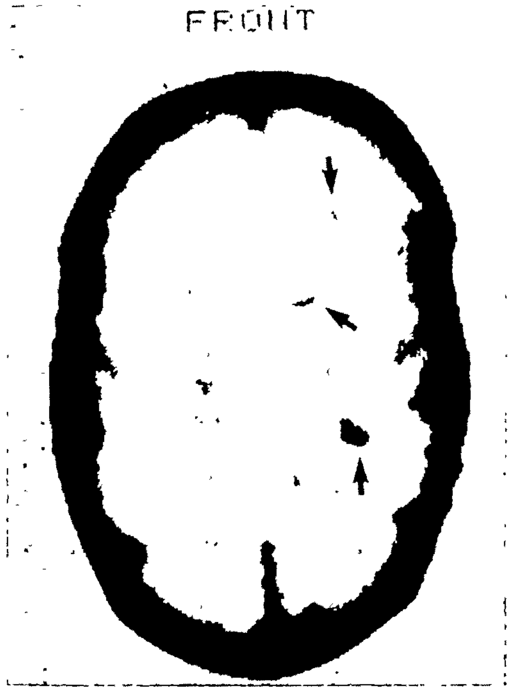

Fig 1b *Computed tomogram seven days after surgery Remaining blood clot is indicated by arrows.*

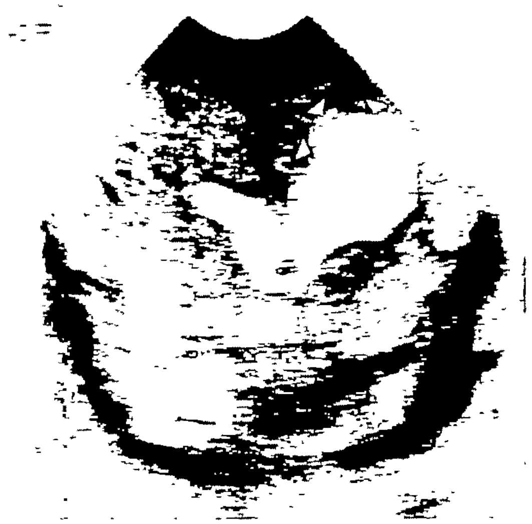

Fig 2 *Coronal ultrasound scan of the brain before discharge home. Note porencephalic cyst at site of original parenchymal haemorrhage on the right side (arrows). Left ventricle is moderately enlarged.*

weak. At 9 months the spastic hemiparesis on the left side became more evident. Head circumference continued to grow along the 25th percentile, and echoencephalography confirmed that the width of the left ventricle and the porencephalic cyst had not increased in size. At 1 year the child was alert, was able to call 'daddy', and attempted to stand. He could walk freely at 16 months with a slight limp in the left leg.

## Discussion

Large intracerebral and intraventricular haemorrhage has been reported to be fatal in 76–100% of cases.[1 2] Virtually all surviving patients have moderate to severe neurological deficits,[1] and up to 58% of them develop hydrocephalus.[1] It is unclear how much of the neurological deficit after such a haemorrhage is due to immediate parenchymal damage and how much is due to hydrocephalus.[1 6] Shunt complications can make matters worse.

Directly evacuating the parenchymal haemorrhage and intraventricular blood clots theoretically reduced two pathogenetic mechanisms. Firstly, pressure reduction alleviated ischaemic damage to the perifocal parenchyma; the rapid neurological improvement of our patient six hours postoperatively might support this. Secondly, evacuation of the blood clots possibly helped to arrest developing hydrocephalus which might have been produced by temporary occlusion of the interventricular foramina. As the dilatation of the ventricles was arrested at a moderate stage, definitive shunting or lumbar punctures were not necessary.

It is impossible to determine whether evacuation of the haemorrhage influenced the outcome at 16 months. Potential benefit of the procedure may be confined to the rapid relief of abnormal neurological signs in the acute stage of intracerebral and intraventricular haemorrhage, or it may also reduce the incidence of progressive post-haemorrhagic obstructive hydrocephalus.

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# Atrial natriuretic peptide and patent ductus arteriosus in preterm infants

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SUMMARY Preterm infants with symptomatic patent ductus arteriosus had considerably raised plasma concentrations of atrial natriuretic peptide. Surgical ligation of the patent ductus arteriosus was associated with an immediate fall in plasma atrial natriuretic peptide concentration. Thus left to right shunting and left atrial distension may cause atrial natriuretic peptide release in preterm infants with patent ductus arteriosus.

The existence of a natriuretic hormone released by atrial distension and volume expansion was postulated more than 30 years ago. Recently such a hormone, atrial natriuretic peptide, was discovered.[1] It is produced by mammalian atriae, stored in granules of atrial myocytes and released into the circulation when volume expands and the atrium distends.[1 2]

Preterm infants with symptomatic patent ductus arteriosus are a good group in which to study atrial natriuretic peptide release. In these infants arterial blood is shunted from the aortic root into the pulmonary circulation leading to an increase in pulmonary and left atrial blood volume and to a considerable rise in left atrial pressure.[3] Thus if atrial distension is a major stimulus for atrial natriuretic peptide release, patent ductus arteriosus ought to be associated with raised concentrations of atrial natriuretic peptide and closure of the ductus should result in a drop in plasma atrial natriuretic peptide concentration

## Methods

Six preterm infants with symptomatic patent ductus arteriosus who required assisted ventilation underwent surgical ligation. The diagnosis of symptomatic patent ductus arteriosus with definite left to right shunting was based on the usual clinical criteria of typical left subclavicular murmur, increased peripheral pulses, radiological evidence of cardiomegaly, and increased pulmonary vascular markings. All infants were also evaluated by two dimensional echocardiography to show the enlarged left atrium and to exclude structural congenital heart disease. Gestational age at birth ranged between 26 and 34 weeks (median 30), birth weight between 850 and 1520 g (median 1175), and age at the time of operation between 7 and 13 days (median 10). Patent ductus arteriosus was confirmed and ligated through a left lateral thoracotomy. At operation, ductal diameter was at least the same as that of the aorta.

A 1·5 ml sample of blood was taken into tubes coated with edetic acid for determination of plasma atrial natriuretic peptide concentration. Routine blood sampling was also done about six hours before operation, and between 16 and 24 hours afterwards. Blood was centrifuged immediately and plasma stored at −20°C until assayed.

For comparison, plasma atrial natriuretic peptide concentrations were measured in 14 preterm infants (gestational age at birth from 29 to 34 weeks, median 30; age at blood collection from 7 to 14 days, median 10). Apart from prematurity they were healthy and did not require assisted ventilation whereas all the infants with patent ductus arteriosus required it throughout the study. Plasma atrial natriuretic peptide concentrations were measured by radioimmunoassay after extraction and corrected for incomplete recovery as recently described.[4] Results were expressed as mean (SD) and statistical comparisons were made by analysis of variance.

## Results

Mean (SD) plasma atrial natriuretic peptide concentration in premature infants with symptomatic patent ductus arteriosus was considerably raised compared with that of age matched 'healthy' preterm neonates, being 379·5 (76·5) and 40·9 (21·7) fmol/ml, respectively (p<0·01).

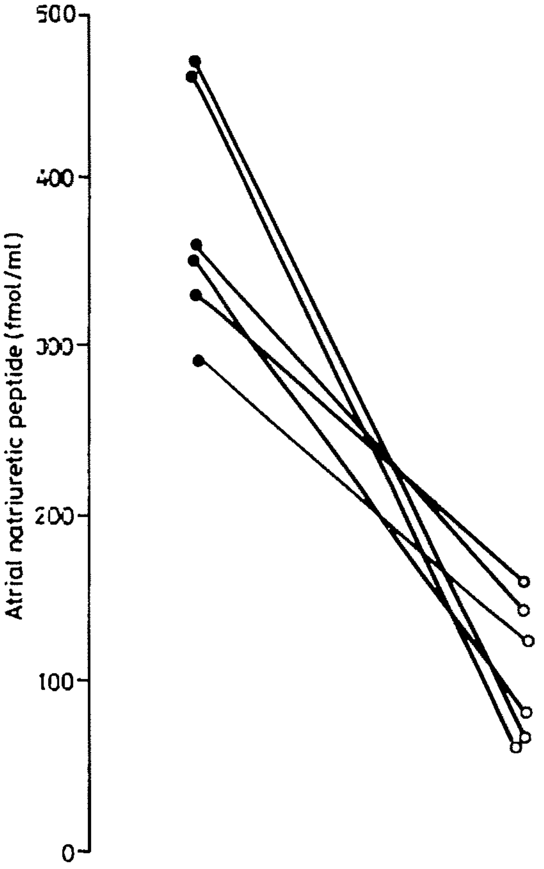

Figure *Plasma concentration of atrial natriuretic peptide in six preterm infants before ● and after ○ surgical ligation of patent ductus arteriosus.*

Surgical ligation of patent ductus arteriosus was associated with a fall of plasma atrial natriuretic peptide concentrations in all six infants (figure). The mean (SD) plasma atrial natriuretic peptide concentration postoperatively was 107·8 (41·2) fmol/ml (p<0·01). Ligation did not influence serum concentrations of sodium (135·0 (5·6) and 135·3 (5·6) mmol/l), protein (47·7 (9·1) and 47·0 (4·7) g/l), or creatinine (1·5 (0·6) and 1·4 (0·5) mg/dl).

## Discussion

Mechanisms by which atrial natriuretic peptide is released into the circulation have not yet been well defined in infants and children. We have recently shown that atrial natriuretic peptide is raised in children with fluid overload due to end stage renal disease when compared with children with chronic renal failure without volume expansion, and with normal healthy children.[4] The association between the fall in atrial natriuretic peptide concentration and decrease in body weight after volume reduction by haemodialysis suggests that in children volume expansion releases atrial natriuretic peptide. In preterm infants plasma atrial natriuretic peptide concentrations are considerably raised on the second day of life and decrease to normal within 2 or 3 weeks of age.[5] Concentrations are raised in premature infants with increased sodium intake and are related to sodium excretion.[6]

The localisation of the sensor of atrial natriuretic peptide release has not yet been clearly defined in clinical studies. Interruption of left to right shunting and decreased left atrial distension by surgical closure of the patent ductus arteriosus seems to be a good clinical model in which to study mechanisms of atrial natriuretic peptide release in preterm infants. The immediate drop in plasma atrial natriuretic peptide concentration by 72% when the ductus is closed in preterm infants may indicate that atrial distension due to left to right shunting is responsible for increased atrial natriuretic peptide release in preterm infants with patent ductus arteriosus.

Raised plasma atrial natriuretic peptide concentrations in preterm infants with patent ductus arteriosus may help to preserve renal function and to antagonise the renal vasoconstrictor hormones that are raised in preterm infants with symptomatic patent ductus arteriosus. Although we did not measure renal function in the present study, indirect evidence (unchanged body weight and stable plasma concentrations of sodium, protein, and creatinine) suggest that an appreciable reduction in urine flow did not occur in our preterm infants after closure of the ductus. This may be due to the fact that renal vasoconstrictor hormone concentrations fall at the same time and renal perfusion improves after abolishing the ductal steal phenomenon.

This study was supported by a grant from the Deutsche Forschungsgemeinschaft (Ra 326/1–2) and HW Seyberth is in receipt of a Heisenberg Stipend from the Deutsche Forschungsgemeinschaft We thank Dr RE Lang, German Institute for High Blood Pressure Research for developing the atrial natriuretic peptide radioimmunoassay and Mrs R Pfohler for technical assistance

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# Intestinal obstruction due to ingested Vaseline

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SUMMARY A case of intestinal obstruction due to ingested Vaseline (white soft paraffin) is described. While intestinal obstruction due to bezoars and impacted foodstuffs is uncommon, though well recognised, we know of no previous reports of obstruction caused by semisolid mineral matter.

## Case report

A 13 month old girl was admitted having swallowed about 50 g of Vaseline. After confirmation from the Regional Poisons Unit that this substance was non-toxic she was observed overnight and discharged home the next day, well and asymptomatic.

The following day she became irritable and unwell, began vomiting, and developed abdominal distension. She was readmitted to hospital four days later, having had no bowel action for two days. Her condition deteriorated and she was then transferred to this unit.

She was obviously unwell, with a temperature of 39°C; she was dehydrated and tachypnoeic with grunting, shallow respiration, and pronounced subcostal and intercostal recession. The abdomen was grossly distended and tympanitic with general tenderness Obstructive bowel sounds were present The rectum was empty and dilated. An abdominal radiograph (figure) showed grossly dilated loops of small bowel. After vigorous resuscitation laparotomy was performed

The entire small bowel was grossly dilated. The large bowel was slightly dilated and there were large clumps of tenacious, solid material in the caecum and transverse colon, but none in the small bowel. The mesenteric glands were enlarged and inflamed, but there was no perforation or peritonitis The bowel was normally rotated and there was no evidence of intussusception, bands, or other causes of obstruction.

The small bowel was decompressed by retrograde stripping. A large amount of gas and bile stained fluid was aspirated through a nasogastric tube. The lumps of Vaseline in the caecum and colon were then milked distally to the rectum. The abdomen was closed and the Vaseline in the rectum washed out with saline through a rectal tube.

Her recovery was uneventful and she was discharged home on the ninth day, by which time she was feeding well and opening her bowels normally.

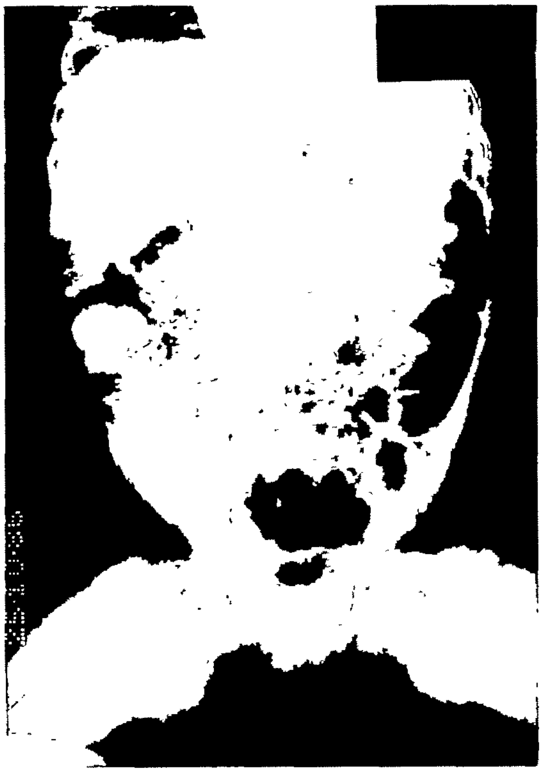

Figure *Abdominal radiograph showing dilated loops of small bowel with opaque masses in caecum and right colon*

## Discussion

Swallowing non-digestible foreign material is a common occurrence, especially in childhood. Most foreign bodies which reach the stomach will pass through the gastrointestinal tract without complications, and surgical intervention is required only in a few cases, even in small infants.[1]

Complications that can arise from failure to pass a foreign body are ulceration, perforation, and obstruction. Ulceration and perforation occur with long, sharp objects. Intestinal obstruction due to ingested foreign material is less common, and usually occurs with bezoars when the amount of material is large and has accumulated over a period of time.[2 3]

Vaseline is a British trade name for white soft paraffin that has been bleached. It is a non-toxic, purified, semisolid mixture of hydrocarbons obtained from petroleum, with a melting point of 38°–56°C,[4] and was initially considered unlikely to cause any complications The enlarged, inflamed, mesenteric glands found at operation suggest that there was an inflammatory response, perhaps as a result of impurities present in the Vaseline. This would account for the clinical signs of fever and abdominal tenderness.

We do not understand why the material (which was able to pass through the small bowel) should lodge in the caecum and colon where the lumen is greater and cause obstruction there. It is possible that absorption of water in the right colon (which is a physiological function) resulted in a tenacious combination of faecal material and Vaseline which proved too much for the bowel peristalsis.

Although not applicable in this particular case because the overt signs of obstruction with peritonism warranted urgent laparotomy, hyperosmolar contrast enema may be used to relieve intraluminal obstruction and should be considered so that laparotomy might be avoided.

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# Perianal infection with group A streptococcus

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SUMMARY Anal fissure in childhood usually heals quickly after treatment with stool softeners and a local anaesthetic ointment; infection does not usually occur. Two cases are reported in which Lancefield group A β haemolytic streptococci were isolated from cultures from the perianal skin, which was erythematous and excoriated.

## Case reports

CASE 1

An otherwise healthy 4 year old boy presented with a three week history of perianal irritation and discharge. At first a white discharge had been noticed on his pyjamas. On closer examination his mother had found small pustules surrounding the anus and a small, immobile white streak which she assumed to be a threadworm. The whole family had been treated with piperazine for a week, but the patient's symptoms had not improved. Miconazole and hydrocortisone cream had produced transient but incomplete relief of the irritation, and the discharge had continued. On examination the perianal region was erythematous and excoriated but no evidence of trauma was found. There was a sticky white discharge from the anus. He was treated with antiseptic baths and an emollient ointment, pending the results of a Sellotape test for threadworm ova (negative) and culture of a perianal swab, which yielded a profuse growth of group A β haemolytic streptococci. An oral course of phenoxymethylpenicillin resulted in prompt and complete recovery.

CASE 2

An otherwise healthy 5 year old girl presented with a three week history of perianal rash, which had initially appeared as tiny, yellow headed pustules. The main symptoms were itching, pain on defecation, and dysuria. There were no other urinary symptoms. Clotrimazole cream had been used for a week with no improvement. On examination there was erythema, excoriation, and fissuring surrounding both the anus and vulva but more obvious around the anus. A Sellotape test for threadworm ova was negative, but group A β haemolytic streptococci were grown from culture of a perianal swab. She was asymptomatic after one week of oral treatment with phenoxymethylpenicillin.

Neither child was systemically unwell, but both had suffered considerable discomfort. Bacterial cultures from other sites were not available. There were no signs of sexual interference.

## Discussion

The duration of symptoms before antibiotics were started together with the prompt response to penicillin indicate that the streptococcus played a true pathogenic part in these two cases.

Group A streptococci have been isolated from the perianal region in both symptomatic[1] and asymptomatic[2] adults. Infections of both the vagina[3] and the perianal area[4] have been reported in children, although streptococcal infection is rarely mentioned in standard textbooks. In the 10 cases of perianal cellulitis due to group A streptococci that were described by Amren *et al* the predominant features were intense erythema and swelling, the skin surface being intact in all but one case.[4] Intense inflammation was also the principal feature in nine preadolescent girls with group A streptococcal vaginitis.[3]

Perianal infection with group A streptococcus in childhood causes considerable discomfort, which may be unduly prolonged without appropriate antibiotic treatment It should be suspected when there is obvious inflammatory change, with or without fissuring or discharge. The cases reported here suggest that the presence of papules at an early stage may also be characteristic. A perianal swab should be obtained in all such cases.

It is important to remain vigilant for sexual abuse. When group A streptococci are not isolated from perianal eruptions organisms related to sexually transmitted diseases should be sought.

I thank Dr Peter Husband for permission to report these cases

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# Muscle carnitine deficiency presenting as familial fatal cardiomyopathy

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SUMMARY Three siblings presented with fatal cardiomyopathy confirmed by electron microscopy, and normal serum but low muscle carnitine concentrations. A fourth had similar signs but remained asymptomatic. He was treated with carnitine orally which increased the concentration in muscle, though it remained below normal. Electron microscopic features were unchanged.

Carnitine deficiency was first described by Engel and Angelini in 1973.[1] Carnitine is a carrier in the long chain fatty acid transport system that is essential for the transport of fatty acids across the inner mitochondrial membrane. Deficiency of carnitine affects mitochondrial oxidation of fatty acids and results in the accumulation of lipids in the cytoplasm.[2]

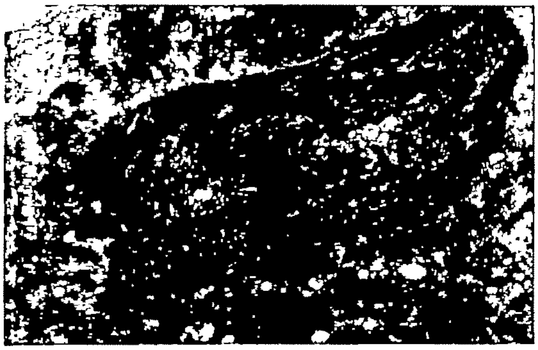

Fig 1 *Electronphotomicrograph of muscle biopsy specimen from case 3 showing a myofibre with central nucleus (×16 500)*

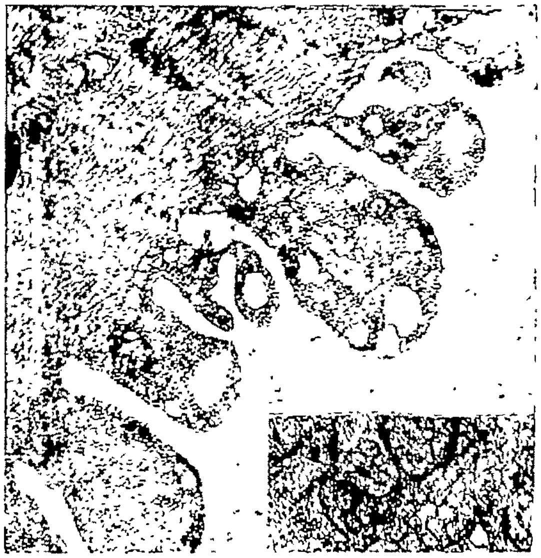

Fig 2 *Electronphotomicrograph of muscle biopsy specimen from case 4 showing irregular folds of sarcolemma. Note presence of small lipid droplets under the sarcolemma and between the myofibrils (×22 100) Inset: cluster of mitochondria with tubular cristae (×32 500)*

We describe a non-consanguinous Sephardic family with two healthy children and three children who presented with fatal cardiomyopathy probably due to muscle carnitine deficiency (fig 1). A sixth and youngest surviving sibling was asymptomatic at

Table *Clinical and laboratory details of the siblings*

| *Variable* | *Case 1* | *Case 2* | *Case 3* | *Case 4* |
|---|---|---|---|---|
| Sex | Male | Male | Female | Male |
| Age at presentation | 3 years | 2 years 4 months | 1 year 6 months | 10 months |
| Presenting illness | Wheezing | Wheezing | Wheezing | Wheezing |
| Age at death | 4 years | 3 years 2 months | 3 years | Alive |
| Cardiac impairment | Right and left heart failure | Left heart failure, arrhythmia | Right and left heart failure | None |
| Chest *x*-ray | Enlarged heart size, decreased pulsations | Enlarged heart size, pulmonary venous congestion | Enlarged heart size, pulmonary venous congestion | Normal |
| Electrocardiogram | Left axis deviation, left ventricular hypertrophy, Q waves in $V_{5-6}$ | Ventricular premature beats, right bundle branch block, Q waves in $V_{5-6}$, ST elevation in $V_{4-5}$ | Left and right ventricular hypertrophy, Q waves and ST elevation in I, AVL, $V_{5-6}$ | Normal |
| Echocardiogram | Not done | Dilatation and hypertrophy of left atrium and ventricle, ejection fraction 0·55 | Biventricular hypertrophy, decreased contractility, thickening of mitral valve | Normal |
| Cardiac catheterisation | Not done | Cardiomyopathy and mitral insufficiency | No anatomic abnormality, decreased cardiac output consistent with cardiomyopathy | Not done |
| Serum glutamic oxaloacetic transaminase activity (normal=≤40 U) | ≤830 | Not done | ≤1100 | Normal |
| Creatine phosphokinase (normal=≤30 u) | Not done | Not done | 34 | Normal |
| Serum carnitine concentration (nmol/ml) (normal=30–60) | Not done | Not done | 51·2 | 28 |
| Muscle carnitine (micromole/g wet weight) (normal: above 1·5) | Not done | Not done | 0·4 | 0·33 |
| Muscle biopsy: haematoxylin and eosin stain | Not done | Not done | Variation in fibre size, increased number of central nuclei, some fibres undergoing phagocytosis | Variations in fibre size |
| NADH and myosin stains adenosine triphosphatase | Not done | Not done | Preponderance of type 1 myofibrils and atrophy of type 2 fibres | Preponderance of type 1 fibres |
| Oil red o stain | Not done | Not done | Enhancement of lipid stain | Increased amount of neutral lipids |
| Electron microscopy | Not done | Not done | Increased number of myofibres with central nuclei, lipid droplets, sarcolemmal folds | Irregular folds of the sarcolemma, small lipid droplets, tubular cristae in mitochondria |

the time of writing but has muscle carnitine deficiency. No clinical muscle weakness was detected in any of the cases.

## Case reports

The table shows the clinical and laboratory details of the four patients. Cases 1–3 died, and case 4 remained asymptomatic. When his muscle carnitine deficiency was diagnosed treatment with oral carnitine (400 mg three times a day) was started. Repeated examination after an interval of four months showed a rise in serum carnitine concentration to 31·2 nmol/ml. Muscle carnitine concentration was 0·9 µmol/g wet weight which, though still below normal, was nevertheless more than double the value before treatment. Histological and electron microscopic examination of the second muscle biopsy specimen were unchanged (fig 2) There was no clinical or laboratory evidence of muscle, heart, or liver disease.

## Discussion

There are two forms of primary genetic carnitine deficiency: systemic carnitine deficiency is characterised by low concentrations of carnitine in both serum and muscle, and muscle carnitine deficiency by low concentrations in muscle but normal concentrations in serum.[2] Serum carnitine deficiency presents most commonly as a syndrome similar to Reye's disease,[2 3] but a familial cardiomyopathy has also been described in which carnitine treatment leads to increased serum and muscle carnitine concentrations and improved cardiac function.[4 5]

Muscle carnitine deficiency usually presents with progressive muscle weakness and is often complicated by cardiomyopathy. Because decreased transport of carnitine into the muscle cell is the pathophysiological defect treatment with oral carnitine is not usually effective.[2] We know of one case report, however, in which a successful clinical response to carnitine was described.[6] Muscle carnitine deficiency presenting as cardiomyopathy without noticeable muscular weakness has not previously been described as far as we know, although respiratory symptoms in children with carnitine deficiency and cardiomyopathy are common.[4 5]

Case 4 had a low muscle carnitine concentration but no clinical evidence of muscle or cardiac disease. This may be due to his being in the preclinical stage of the disease, but heterozygosity as the cause of the benign course cannot be excluded. Another possibility is that he was responding to treatment as the muscle carnitine content increased. The histopathological picture, however, did not improve over four months.

The possibility of congestive cardiomyopathy being the only sign of muscle carnitine deficiency makes estimation of muscle carnitine concentration desirable in all cases of undiagnosed cardiomyopathy. Biochemical studies of muscle specimens obtained by needle biopsy are currently widely used and relatively easy to perform.

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# Glossal cysts in four infants

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SUMMARY Cysts at the base of the tongue causing stridor may be fatal if they are not recognised and treated. Digital palpation along the surface of the tongue to the epiglottis is a useful diagnostic method. An operative technique that might avoid the need for tracheostomy is described.

Cysts at the base of the tongue are a rare cause of stridor in infancy and may cause death if they are not treated. Tense midline swellings immediately superior to the epiglottis, they cause chronic or recurrent stridor, which usually starts soon after birth. We describe four infants with glossal cysts who were seen at this hospital between April and December 1985.

## Case reports

CASE 1

A 4 week old boy was referred with pneumonia, diagnosed on the basis of two days of cough and shortness of breath, and fever, tachypnoea, chest indrawing, and crepitations. The mother had noted noisy breathing and vomiting since birth. On examination the child was noted to have inspiratory stridor. A tense midline cyst measuring 1·5×1·5 cm was palpated just superior to the epiglottis by inserting the fifth finger along the upper surface of the tongue (figure). Direct laryngoscopy confirmed the presence of a cyst at the base of the tongue; it obscured any view of the epiglottis or vocal cords.

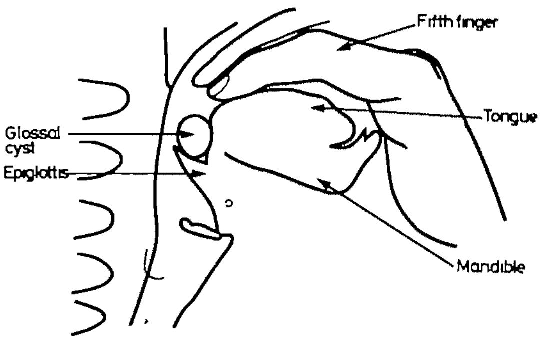

Figure *Direct palpation of glossal cysts*

A tracheostomy was performed under local anaesthesia. The cyst was incised yielding a viscous milky mucoid fluid and an endotracheal tube was easily inserted before the cyst was deroofed. A tongue traction stitch was inserted in the hope that should postoperative swelling obstruct the upper airway the obstruction would be relieved by pulling the tongue forwards. This technique failed and tracheostomy was required for four days postoperatively.

CASE 2

A 4 month old boy was referred with a history of several episodes of 'blocked nose, hoarse cry, and severe pneumonia.' Examination showed a well child with no respiratory signs. Direct palpation of the tongue and direct laryngoscopy showed a cyst identical with that in case 1. At operation needle aspiration of the cyst without anaesthetic again yielded milky viscous fluid. An endotracheal tube was inserted and after some difficulty finding the roof of the deflated cyst it was excised. A tongue traction stitch was inserted because of postoperative stridor; this settled over three days.

CASE 3

An 18 month old girl was referred with a history of stridor since birth She had had three previous admissions to rural health centres with 'pneumonia.' A fifth finger inserted along the surface of the tongue, but not as far as the epiglottis, failed to palpate the cyst. It was later diagnosed by direct laryngoscopy under general anaesthesia. Cystectomy was difficult to perform and a tracheostomy was required for six weeks

CASE 4

A 3 month old boy was admitted with a diagnosis of upper respiratory infection and a blocked nose. Stridor was immediately apparent and a cyst identical with those in the previous cases was detected by palpating along the surface of the tongue The mother refused a tracheostomy and the child died suddenly of acute upper airways obstruction three days later.

## Discussion

Cysts arising from the dorsal surface of the tongue may present with stridor, feeding difficulties, symptoms of inhalation, and respiratory distress[1] Some arise from thyroglossal remnants and some are simple mucus retention cysts. Thyroglossal cysts at the upper end of the developmental tract occur in the region of the foramen caecum. Mucus retention cysts typically occur in the groove between the tongue and epiglottis; the cysts reported here were probably of this last kind.

Although these cysts are rare, they can be easily diagnosed. The technique of inserting the little finger along the surface of the tongue has been recommended in the routine examination of children with chronic or recurrent stridor,[1] although it is not mentioned in standard paediatric textbooks. Palpation of a tense cyst by the little finger produces an unmistakable sensation. We have shown the usefulness of this technique, although, as case 3 illustrates, palpation must extend to the epiglottis to avoid missing the cyst.

We encountered several perioperative problems. They included airways obstruction during induction of anaesthesia and postoperatively, and difficulties in finding the roof of the cyst once the contents had been aspirated. We therefore propose the following operative method: an anaesthetic that can be inhaled should be given, and a traction stitch placed in the tongue. Pulling the tongue forward should relieve upper airway obstruction Once the child is paralysed a holding stitch should be inserted into the cyst roof to allow the contents to drain and facilitate endotracheal intubation and simple marsupialisation. Postoperatively the tongue stitch should remain taped to the face until all stridor has resolved. This may avoid tracheostomy with its potential for serious complications in this age group.[2 3] Preoperative tracheostomy with local anaesthesia should be considered in hospitals without an experienced paediatric anaesthetist. A vertical rather than a transverse incision is preferable for urgent tracheostomies because deviation from the midline is less likely to occur.[2 3] The cosmetic result is quite acceptable.

The occurrence of four cases of glossal cysts in a nine month period in a population of about 300 000 may be a coincidence. Glossal cysts have not previously been reported from Papua New Guinea and paediatricians and surgeons with considerable experience in the country have not seen a case (JKA Cleary *et al*, personal communication), but previous cases could have been misdiagnosed as pneumonia, which is a common cause of death in this community.

The authors acknowledge the help of Dr F Shann and Professor PD Phelan in preparing this manuscript

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# Cellular phosphate in renal tubular acidosis

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SUMMARY In two infants with distal renal tubular acidosis phosphate depletion was observed in the extracellular and intracellular compartments of the erythrocytes. Treatment corrected this disturbance over a period of several months. Cell phosphate deficiency may contribute to the adverse effects of renal tubular acidosis on bone.

Distal renal tubular acidosis is characterised by low serum concentrations of bicarbonate, raised serum concentrations of chloride, sustained metabolic acidosis and inadequate urinary acidification (pH >6). In addition to hyperchloraemic acidosis, there is often a variety of associated disturbances in electrolyte metabolism like hypokalaemia and hypercalciuria. The clinical manifestations of these abnormalities may include muscle weakness, osteomalacia or rickets, growth retardation, and nephrocalcinosis

This study follows the metabolic changes of phosphate in and out of the red cells, at both the acidotic stage and during treatment

## Patients and methods

Two preterm infants (small for dates) with gestational ages of 34 and 32 weeks and birth weights of 1100 and 1130 g, respectively, were studied. Both neonates had previously been treated for late metabolic acidosis. The recurrence of acidosis in both infants at nine and 12 weeks after birth led to the diagnosis of hyperchloraemic acidosis and sodium bicarbonate was readministered.

We measured serum calcium concentration by titration against edetic acid (Calcette model 4008, Precision System Inc, Massachusetts, United States). Alkaline phosphatase activity, adenosine triphosphate, and 2, 3 diphosphoglycerate concentrations were measured photometrically with kits from Boehringer and Sigma Inorganic phosphate concentration in plasma and red cells was also measured photometrically by the method of Challa *et al.*[1] Serum concentration of potassium was measured by flame photometry, serum bicarbonate with a pH blood gas analyser (Acid Base Laboratory, Radiometer, Copenhagen), and serum chloride with the photometric method of Zall *et al.*[2]

## Results

The figure shows that the bicarbonate concentrations were low at the time of diagnosis (6 and 15·5 mmol/l, respectively) and took about two months of treatment to be corrected. The chloride concentrations took far longer to be corrected and even after a year's treatment the values in both infants were in the upper limit of normal.

Serum concentration of calcium was low before treatment (2·13 and 1·78 mmol/l, respectively); administration of bicarbonate and 0·3 µg/d 1α hydroxyvitamin $D_3$ ($1\alpha OHD_3$) in the first week of treatment increased it. The dose of $1\alpha OHD_3$ was gradually lowered to a maintenance dose of 0·05 µg/d. Plasma concentrations of inorganic phosphate were also low at diagnosis (1·43 and 1 03 mmol/l, respectively) and were corrected slowly over about two months The erythrocytes of these infants were found to be depleted of inorganic phosphate, with concentrations at the time of diagnosis of 0·26 and 0·43 mmol/l (normal range 0·80–1·13 mmol/l) After administration of alkaline solutions they started to recover slowly, taking less than two months in the first case and over six months in the second

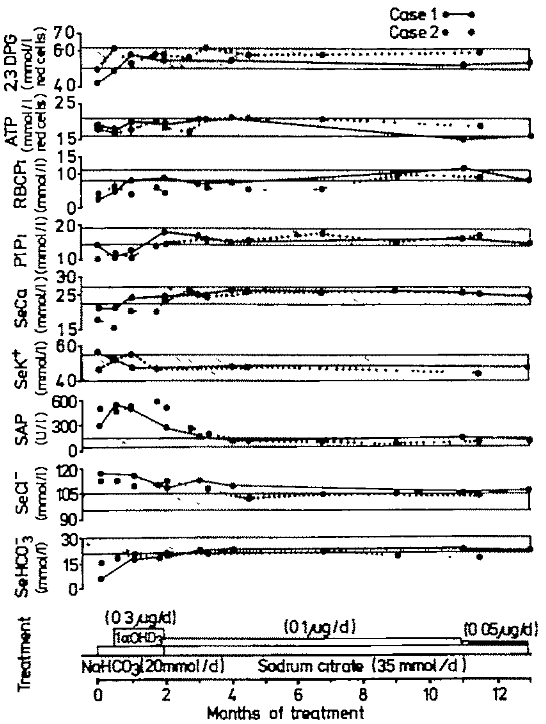

Figure *Concentrations of bicarbonate ($HCO_3^-$), chloride ($Cl^-$), alkaline phosphatase (SAP), potassium ($K^+$) and calcium (Ca) in serum, inorganic phosphate in plasma, and red cells (PlPi and RBCPi) and red cell ATP and 2,3 DPG of two cases with renal tubular acidosis before and during treatment*

Alkaline phosphatase activities were high at diagnosis in both cases but became normal within four months of treatment. The concentration of organic phosphate from adenosine triphosphate (ATP) in red blood cells was normal at the time of the diagnosis, when the cells were depleted of phosphate and did not change all through the study Concentrations of 2,3 diphosphoglycerate were low normal or low at diagnosis and increased after the administration of bicarbonate.

## Discussion

Although it is well established that acidosis may result in the liberation of phosphorus from organic compounds within cells, this hyperphosphataemia has been described in association with lactic acidosis. Other data suggest that ammonium chloride induced acidosis is not associated with increases in plasma phosphorus.[3]

In the two infants we studied with renal tubular acidosis phosphate depletion was found both extracellularly and inside the red blood cells; depletion may have been found in other cells as well. Preston *et al* reported depletion in red blood cells, leucocytes, and platelets in an adult case of proximal renal tubular acidosis.[4] The intracellular changes in the case and the two we studied were more extensive than the extracellular ones and there was a time lag for repletion between the two compartments after treatment. Plasma inorganic phosphate returned to normal long before the chloride ion concentrations and the alkali reserves approached normal limits In contrast, intracellular inorganic phosphate started repleting at a lower rate and in the second infant took up to six months before it was in the normal range. It is worth noting that this infant was diagnosed at a later stage (3 months) when the alkaline phosphatase was very high (500 IU/l; normal range 35–100) and remained high for a longer period than in the first child.

Despite the intracellular and extracellular inorganic phosphate depletion the ATP concentrations in the erythrocytes of the two cases did not show any significant changes and were within the normal limits. These findings were at variance with those of Preston *et al*, who found an initial decrease in ATP that was corrected after a month of treatment.[4] He attributed this fall to intracellular acidosis due to potassium ion losses that had been exchanged with hydrogen ions. Acidosis inhibits glycolysis and consequently ATP production. In the two infants that we studied the plasma concentrations of potassium changed but were within the normal range. Another reason for these results might be that their study was of a chronic case of renal tubular acidosis in an adult who had also developed osteomalacia and muscle weakness

Changes in pH also affect the concentrations of 2,3 diphosphoglycerate because acidosis leads to a fall and alkalosis to a rise of this metabolite. In our two cases the concentrations of 2,3 diphosphoglycerate were low normal or low at diagnosis and became normal within a month of treatment. In the patient described by Preston *et al* the recovery of the concentration of 2,3 diphosphoglycerate took far longer (> four months).

Serum concentration of calcium was abnormally low in the second infant and low normal in the first but recovered after several weeks of treatment. As has been reported in the past increased rates of acid production are accompanied by positive acid balances, increased urinary excretion rates, and negative calcium balances. The urinary losses of calcium that accompany increased rates of fixed acid production are the consequence of reduced net renal tubular calcium reabsorption that seems to be independent of parathyroid hormone and vitamin D.[5]

The mechanisms by which augmented fixed acid production rates stimulate net bone resorption are not yet fully defined as the activation of the parathyroid hormone/vitamin D endocrine system does not mediate the effect of acidosis. Bone resorption must be either stimulated by direct effect of acidosis or as a consequence of some as yet undefined humoral mechanism.[6]

Although no radiological findings of rickets were evident, the alkaline phosphatase activities were abnormally high in both infants but started to become normal after treatment Phosphate depletion in cells might be one factor for disturbing bone metabolism, which is reflected in the high activities reported.

From a clinical point of view late metabolic acidosis in small birth weight neonates should always be investigated for the pathological cause of origin

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# Oral desmopressin in neonatal diabetes insipidus

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SUMMARY A neonate with cranial diabetes insipidus was successfully treated with oral desmopressin. The patient had a midline cleft lip and palate and we obtained a more consistent response using the oral route than using the usual nasal route.

Desmopressin has been the treatment of choice for cranial diabetes insipidus since its introduction in 1972.[1] It is usually administered through the nose by nasal catheter or spray, but in a neonate with gross deformities of the oral and nasal cavities it is difficult to maintain a consistent response using this route.

## Case report

A female infant was born at 38 weeks' gestation, birth weight 2060 g (<third centile), with a midline cleft lip and palate. The cleft extended into the left nostril and there was free communication between the oral and nasal cavities to either side of an apparently well formed nasal septum. Her head circumference was 29·0 cm. (<third centile); there were no other dysmorphic features.

The baby fed well at the outset on formula milk. At the age of six days she developed bilateral purulent conjunctivitis due to simultaneous gonococcal and chlamydial infections. This was successfully treated with frequent saline washouts, intravenous cefotaxime, oral erythromycin, and topical tetracycline. On day 8 she was noted to be hypernatraemic, the plasma sodium concentration rising to 158 mmol/l by day 12, but with normal concentrations of potassium and urea. At this time the plasma osmolality was 319 mOsm/kg $H_2O$ when the urine osmolality was 65 mOsm/kg $H_2O$ on a random sample.

Oral intake was by now more than 230 ml/kg/day and urine output greater than 100 ml/kg/day. Cranial diabetes insipidus was provisionally diagnosed and confirmed by giving desmopressin 400 ng intramuscularly after which the plasma sodium concentration fell from 164 mmol/l to 135 mmol/l, the plasma osmolality fell from 329 mOsm/kg $H_2O$ to 284 mOsm/kg $H_2O$ and the urine osmolality rose to 156 mOsm/kg $H_2O$ from 65 mOsm/kg $H_2O$.

Treatment was started with desmopressin intranasally 1 μg twice daily through the intact nostril, but the child's facial anatomy made it difficult to administer with accuracy and consequently her weight varied greatly from day to day. Hypernatraemia persisted and urine output remained excessive (fig 1).

At the age of 33 days desmopressin was given orally in a dose of 5 μg daily, increasing to twice daily to control her urine output adequately. On this regimen weight gain was appropriate (fig 1), and the plasma electrolyte concentrations and osmolality returned to normal. Urine osmolality was measured on all specimens passed over a 24 hour period, and the results suggested that the duration of action of the oral desmopressin was about six hours (fig 2).

Because of the presence of a preservative, chlorbutol 0·5%, in the nasal preparation we at first decided to use the injectable solution by the oral route. There are, however, no reports of adverse effects from enterally administered chlorbutol and therefore we changed to using the nasal solution. This preparation comes in oversized phials containing 2·5 ml (250 mg) of desmopressin which was diluted to 10 ml with physiological saline. Using an oral syringe, 0·2 ml (5 μg) of the solution was given

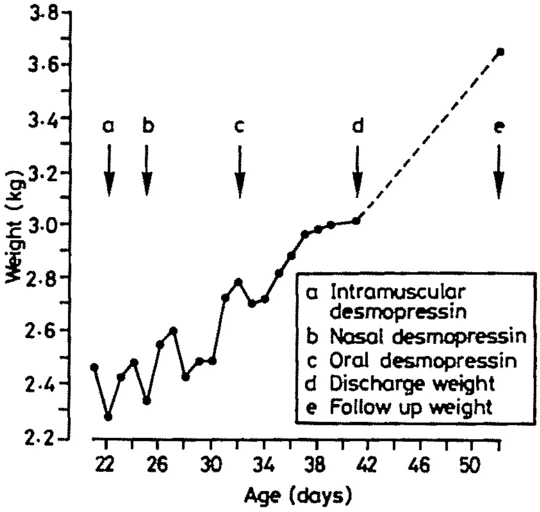

Fig 1 *Daily weight after treatment with desmopressin.*

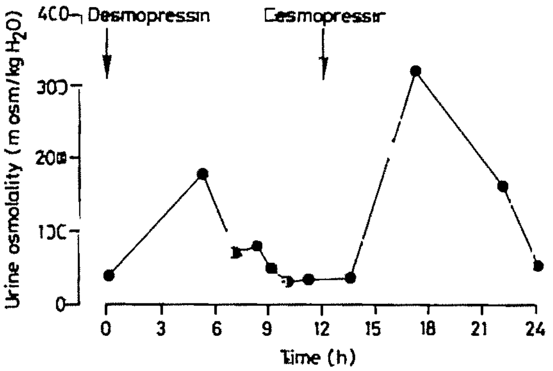

Fig 2 *Effect of oral DDAVP on urine osmolality Times of passing individual urine samples (●), time oral desmopressin given (↓).*

into the oropharynx twice daily. This dose is about 10 times greater than the appropriate nasal dose.

Electrolyte concentrations remained within normal limits and she was discharged at the age of 41 days weighing 3140 g. At follow up at the age of 52 days plasma electrolyte concentrations were normal and she weighed 3660 g.

During her admission a computed tomogram of the brain showed that anteriorly the ventricles were poorly formed and the falx was absent. The cerebral hemispheres, corpus callosum, and cerebellum looked normal Plasma concentrations of cortisol, thyroxine, and thyroid stimulating hormone were within normal limits.

## Discussion

Pituitary hormone deficiencies in association with midline facial defects have been well described, in particular septo-optic dysplasia, the holoprosencephaly spectrum.[2] [3] Our patient had an extensive midline facial cleft with evidence from computed tomography of an intracranial midline defect.

Although the use of oral desmopressin has been reported in older children with cranial diabetes insipidus,[4] we could find no reports of its use in neonates. In our patient oral desmopressin proved successful in maintaining normal plasma electrolyte concentrations and weight gain in the first months of life.

Although the effect of the oral desmopressin in the dose used seemed to last only about six hours we decided not to increase the size or frequency of the dose. This was to avoid water accumulation because plasma electrolyte concentrations and weight gain were normal The period during which free water clearance remains negative can be expected to be prolonged by increasing the size of the oral dose.[4]

Although there was no evidence of other hormonal deficiencies in our patient, her pituitary function will be investigated.

The cost of the nasal preparation is about five times less than that of the injectable formula, but in neonates with cranial diabetes insipidus requiring treatment with desmopressin, the oral route is an effective alternative if the nasal route proves difficult to use.

We thank the nursing staff of the Princess Anne Hospital, special care baby unit for collecting specimens, and Mrs ED Stick for typing the manuscript

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# Effect of pancuronium and pethidine on heart rate and blood pressure in ventilated infants

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SUMMARY To investigate cardiovascular effects in 32 ventilated neonates, given either pancuronium or pethidine, computer based data were analysed for five minutes preceding and for 20 minutes after administration of the drugs. Heart rate and direct mean arterial pressure remained unchanged but arterial pressure variability decreased with each drug.

Pancuronium, a competitive, non-depolarising, neuromuscular blocking agent is often used in conjunction with mechanical ventilation in newborn infants. It may have atropine like side effects. Increases in heart rate and blood pressure in both children and adults have been reported.[1] As would be expected with less vagally modulated hearts, studies generally show no change in infants' blood pressure though tachycardia has been reported.[2] There has been one anecdotal report of hypotension in association with pancuronium[3] but there is no pharmacological basis for this effect as ganglion blockade and histamine release are negligible.[1] Theoretically changes in intrathoracic pressure associated with removal of spontaneous breathing effort may, however, decrease venous return and cardiac output; these in turn may lead to hypotension if ventilator settings are not appropriately adjusted, particularly in the presence of hypovolaemia

Opiates are also recommended to facilitate ventilation, and pethidine (a synthetic opiate) is extensively used in our unit Though it may produce transient orthostatic hypotension, studies have shown no effect on heart rate or blood pressure in supine unanaesthetised adults,[4] though a reduction in both was seen in anaesthetised patients.[5] We know of no relevant published reports concerning neonates.

We have investigated the possible adverse cardiovascular effects of these commonly used drugs and their influence on blood pressure instability using data recorded on a microcomputer.

## Patients and methods

Thirty two infants admitted to the neonatal unit at this hospital were enrolled in the study. All were being ventilated for respiratory distress syndrome and had an umbilical artery catheter in the thoracic aorta (Neocath Biomedical Sensors Ltd, High Wycombe, Buckinghamshire) None had received any drug except vitamin K and no colloid had been given in the hour preceding the study; skin perfusion, capillary filling. and urine output indicated normovolaemia. Procedures likely to affect the measurements were not carried out in the 15 minutes before, or during the study time of 20 minutes. The infants were each given a first dose of either pancuronium (0·1 mg/kg) or pethidine (standard analgesic dose 1·0 mg/kg) to assist ventilation after independent assessment by house officers, the study being complete when there were 16 consecutive infants in each group The mean weight of those receiving pancuronium was 1100 g (range 640–2500) and the mean gestational age was 28 weeks (range 25–33). In the group receiving pethidine the mean weight was 1000 g (range 480–1800) and mean gestational age 28 weeks (range 25–31).

Blood pressure signals from a transducer (Medex MX800, Medex Inc, Haslingden, Rossendale, Lancashire) coupled to the umbilical artery catheter of each infant were relayed to a neonatal monitor (Model 431A Tektronix Ltd, Harpenden, Hertfordshire) that was interfaced with an analog digital converter and Apple IIe microcomputer. This method was chosen in preference to intermittent recording to produce the detail and continuity of a chart recorder but with more flexibility for storage and analysis of the data. Machine code software was designed to collect waveforms over a 20 second period and derive the heart rate, systolic pressure by averaging the peaks, and true mean arterial pressure (MAP), by analysis of the waveforms (digitising rate 50/second). When considering the effect of the drugs, MAP values were compared, MAP representing the complete cardiac cycle and forming the basis of cerebral perfusion pressure calculation. As the waveforms were undamped, judged by the presence of a dicrotic notch, systolic pressure was accurate and used to derive the coefficient of variation as a measure of blood pressure instability based on the formula: coefficient of variation= [standard deviation/average systolic pressure]

×100%/20 second collecting phase. This required less microprocessing time than making calculations based on MAP.

The records of heart rate, MAP, and coefficient of variation, together with a marker when the drug was administered, were stored (time intervals being indicated) on floppy discs, one to two records per minute being derived, 20 seconds sampling time/20 seconds processing time for each cycle.

## Results

The records were averaged for the five minutes preceding then at 0 to 5, 5 to 10, 10 to 15, and 15 to 20 minute intervals after the drug had been given (figure). As there were one or two original data points a minute, each derived data point represented about seven values. Using the unpaired *t* test we found no significant differences between the pre-dose values of heart rate, MAP, or coefficient of variation between the groups. Analysis of variance showed no significant changes in heart rate or MAP after the dose of pancuronium or pethidine, though there was a tendency for heart rate to rise with pancuronium and fall with pethidine. A significant reduction ($p<0.001$) was observed in the coefficient of variation of systolic arterial pressure at each time point after pancuronium (from 5·0% to between 1·9% and 2·6%) and after pethidine (from 5·8% to between 4·0% and 4·3%).

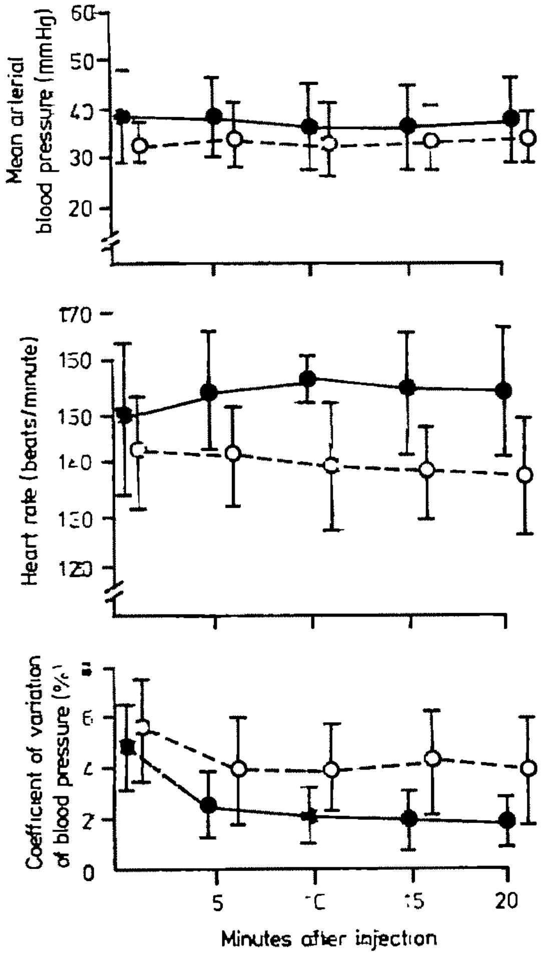

Figure *Effects of pancuronium (—●—) and pethidine (--○--).*

## Discussion

Fluctuation of MAP and cerebral blood flow velocity may be associated with periventricular haemorrhage in preterm ventilated infants, and stabilisation may reduce the incidence.[6] In this study both pethidine and pancuronium reduced fluctuation in MAP with no significant change in heart rate or MAP: thus they can both be used in ventilated infants without increasing the risk of cerebral ischaemia. After the administration of pancuronium the heart rate did not rise to the same extent as in children and adults, presumably because there is less vagal tone in neonates. There was a highly significant fall in coefficient of variation after the administration of both drugs (from 5·0% to an average of 2·1% after pancuronium and from 5·8% to an average of 4·1% after pethidine).

We thank Mr J Messegeur for his invaluable help with software and Mr V [illegible]ber for statistical advice.

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# Red child syndrome

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SUMMARY An acute overdose of rifampicin in an 18 month old white infant is described. The characteristic signs of the syndrome: orange-red discolouration of the skin, urine, and tears, facial pruritus, and periorbital oedema were present and the outcome was uneventful. Paediatricians should be aware of this peculiar yet easily identifiable syndrome.

Toxic reactions to an overdose of rifampicin have been well described in a few adults,[1 2] an adolescent girl,[3] and in 19 children in a day care centre [4] Excluding one death associated with an extremely high overdose (60 g)[2] all the other cases had uneventful outcomes. As far as we know this is the first report of the 'red child (man) syndrome' described in European paediatric literature.

## Case report

An 18 month old white girl was brought to the emergency unit because of intense facial glow and pruritus, severe periorbital oedema, and generalised orange-red discolouration of the skin and urine. Her mother was being treated for pulmonary tuberculosis and the infant was being regularly treated with rifampicin because of a positive tuberculin patch test. Three and a half hours before admission she had been found playing with an empty bottle of rifampicin, which should have contained about 100 ml of a 2% suspension (2 g). One hour later facial glow and pruritus appeared, and in the next two hours rapidly increasing periorbital oedema was noticed. As the whole body skin, urine, saliva, and tears progressively appeared with an orange-red discolouration she was brought to the hospital.

On admission she was apparently well, alert, and had no other abnormal signs During her hospital stay she passed red stools of normal consistency and had no vomiting or fever. Her haemoglobin concentration was 113 g/l and the white cell count was $22\cdot9\times10^9$/l with 66% neutrophils; glutamic oxaloacetic transaminase activity was 20 U/l. She was discharged 12 hours later. The signs and symptoms persisted for a further 24 hours, periorbital oedema disappearing first.

When she was re-examined one month later she had no complaints and was in good health. Plasma protein concentration, serum transaminase, lactic dehydrogenase, $\gamma$-glutamyltranspeptidase, and alkaline phosphatase activities were all within normal limits.

## Discussion

The syndrome due to an acute overdose of rifampicin is still unlikely to be recognised by many paediatricians. In the case reported here the association between rifampicin intake and orange-red discolouration of the skin, urine, and tears was strongly suggested by the history given by the mother. The severe periorbital oedema and the facial pruritus (two of the signs of rifampicin toxicity), however, were not recognised as such by the attending paediatrician who ascribed them to an allergic reaction.

Rifampicin has an important place in the treatment of tuberculosis as well as in the prophylaxis of meningococcal infection. More recently it is also being recommended for the prevention of *Haemophilus influenzae* type b disease.[5] Therefore an increase in the number of cases of accidental rifampicin overdose intake must be expected. In the experience of our emergency unit identification of the drug in acute drug intoxication has not been possible in one fifth of the cases (J Sequeira, personal communication)

We thank Dr Rosa Gouveia for her help in preparing the English version of this manuscript

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# Management of sexual abuse

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In the United Kingdom we are witnessing the beginning of an explosive epidemic of reported cases of the sexual abuse of children. A similar epidemic started 15 years ago in the United States. There is little doubt that this has arisen because of greater public and professional awareness and willingness to intervene in a problem that has been well known for generations.[1 2]

Recent research on both sides of the Atlantic has shown that as many as one in three to one in 10 children—boys and girls—are sexually abused in some way during childhood or adolescence. This research has recently been well reviewed.[3]

While professional awareness is increasing, so too is denial—still the major obstacle to effective intervention. It is true that professionals are often ill equipped to manage sexual abuse in children and are learning to cope only slowly. There are also many difficulties—medical, social, and legal—in this complex area.

Paediatricians have developed skills in the diagnosis and management of physical abuse (non-accidental injury), as well as neglect, and failure to thrive. It seems natural, therefore, that they should also become involved in the management of sexual abuse using their own skills in addition to the new forensic skills needed.

We would like to see paediatricians become increasingly concerned, and children interviewed and examined in hospitals or health centres, and not in police stations where they have been examined in the past.

For paediatricians to become involved is logical, because the complex nature of the symptoms of the sexually abused child implies that many children will present with undisclosed abuse—with genital or anal symptoms, psychosomatic, emotional, or behavioural complaints—and because of problems in development or educational attainment. Paediatricians deal daily with these problems and will increasingly recognise the sexually abused child who presents in this way, for wherever there are children there is sexual abuse of children, and sooner or later the paediatrician will find him or herself confronting a problem which is suspicious or diagnostic of sexual abuse. Confidence in the process of management will encourage intervention on behalf of the child.

## Preparing the ground: the multidisciplinary system[4]

Multidisciplinary cooperation is mandatory in treating this, and other forms of abuse. The professional disciplines usually will be medicine, social work, the law, and the police. Most cases will require support for the child and family, including help from psychologists, child psychiatrists, and social workers. Others include school nurses, health visitors, nursery workers, teachers, and youth workers. Care workers, including foster parents and residential home staff, must also participate in planning for the individual child. Court and probation officers, and those concerned with the perpetrators (including judges and magistrates) are vital links in helping the child. Of the professional workers focusing on the child, the paediatrician and the child's guardian ad litem have major roles.

The nature of sexual abuse within the family often leaves the child unprotected by the mother, and others may have to take responsibility for the child. For the paediatrician to become accepted within the professional network that manages these children he or she will need to develop links and contacts, preferably before handling too many cases. In Leeds a multidisciplinary monthly meeting was organised in 198[illegible] so that interested professionals from all these groups could discuss a number of important issues concerning the response to sexual abuse that would be made in Leeds.

The issues were:

1 The definition of sexual abuse, including the use of a common language and fluency with sexual vocabulary. Overcoming the usual inhibitions about discussing sexual matters and sexual abuse was a major goal.
2 The development of clear management plans for definite and suspicious cases.
3 The development and use of new and existing procedures in cases of child abuse, including case conferences and registration.
4 The diagnosis, including medical examinations, collection of evidence, and interviews.
5 The further management of the child and family.
6 The response to the abusers/perpetrators.
7 The cost and staffing and the need for additional resources

3 A multidisciplinary training programme
The working party reported to the local area review committee, the multidisciplinary forum which carries responsibility in each area of the United Kingdom for dealing with child abuse

We consider that each area will need to establish a small working group to formulate local policy and procedures. The police were included in all our discussions, but it is vital that a policeman with sufficient seniority to influence force policy attends. In our case we were unsuccessful, and the officers who attended were usually of the rank of inspector.

## Paediatrician's role

There are five main areas in which the paediatrician must play a part: diagnosis and reporting; obtaining legal advocacy for the child; counselling and help for the child and family, participation in management through case conferences and reviews, and training personnel and developing services. Contact with secondary care physicians (in addition to the usual ones with primary care doctors working in general practice and the child health service) are important in child and adult psychiatry, paediatric surgery, genitourinary medicine, and occasionally pathology and gynaecology.

Table *Principal indicators of sexual abuse**

**Presumptive indicators:**
- Direct report from child
- Sexually transmitted disease
- Pregnancy
- Genital or anal trauma

**Possible indicators:**
- *Preschool—*
  - Inappropriate or excessive sexual interest, masturbatory activity
  - Genital or anal inflammation, discharge, bleeding, or pain (also apparent pain on sitting or walking)

**Non-specific behaviour and clinical symptoms:**
- *Preschool—*
  - Excessive clinging
  - Sleep disturbance
  - Encopresis or enuresis
  - Abdominal pain, headaches
  - Sudden changes in behaviour
- *School age—*
  - Decrease in performance
  - Truancy
  - Enthusiasm for attendance even when ill
  - Conversion hysteria
  - Anxiety, depression, obsession
  - Change in appetite
  - Sleep disturbance
- *Adolescence—*
  - Antisocial behaviour
  - Truancy, running away
  - Depression, poor self-esteem
  - Drug abuse
  - Self injury or overdose
  - Promiscuity or prostitution
  - Anorexia or obesity
  - Overt concern about pregnancy
  - Adoption of mother role

*This list is not exhaustive, and some seriously abused children will show none of these indicators, effectively concealing the abuse

## Diagnosis

Diagnosis traditionally follows case history, examination, and in some cases laboratory investigation. Most children are seen as outpatients, although brief admission to hospital may be necessary for further investigation and protection in selected cases where the circumstances are not clear.

Children should be seen in comfortable and pleasant surroundings, with space and toys. Plenty of time should be allowed but there is rarely enough, most of it being taken up in discussion and counselling Children are often talked to away from parents, and the layout of the room should take this into account, avoiding the need for parents to return to a general waiting area.

The case history should include an enquiry for common symptoms of abuse and the other conditions in the differential diagnosis Details of any disclosure should be recorded and the child helped to discuss with the doctor what has happened. Notes are best made concurrently or immediately afterwards, if possible. Defence lawyers and judges often check on this point. We always attempt to obtain as much information as possible from other agencies before seeing the child to build a complete picture.

## Types of referral

Referrals follow direct disclosure by the child, or suspicion of abuse by a relative or caregiver, or by an unrelated third party who may be a professional. The reason for referral by a professional may not have been explained to a parent, and this can lead to difficulties in the consultation. Children who are relatives or friends of an abused child, or who have been in contact with a known offender, are also referred. In general, frank and honest discussion of the possibility of sexual abuse is the best policy. Sometimes, however, the doctor may wish to feel his way gradually, to see what information emerges, and approach the subject of sexual abuse indirectly ('sometimes I see children who are wetting because someone has molested them—I always need to check with every child with this problem whether that could have happened to them').

Alternatively, the doctor may wait to discuss sexual abuse until after the examination, investigation, or at a subsequent follow up appointment after other diagnoses have been excluded

Premature action or discussion about sexual abuse can be distressing and threatening to the family. This may result in the family withdrawing and 'pulling down the shutters' in a way that adversely affects future management and follow-up. If suspicion is unresolved it may be better to develop a plan for supervision and follow up with others working with the child and family, thereby maintaining the concern at a professional level.

## Talking to children

Much of the evidence in cases of sexual abuse comes from the child's history Most paediatricians enjoy talking to children, but may feel uncomfortable talking to children about sexual matters in general, and few doctors would be able to talk about sexual abuse without feeling upset. Our former teacher, Dr Michael Buchanan, said, 'with all this talk of sex you would have to be an icicle to be unmoved'.

The approaches vary and there is no single ideal method. Some lawyers judges, and policemen suggest that you can talk to children as though interviewing an adult, as well as avoiding leading questions All who work with children know that this is impractical and that it can be confusing and unrealistic to a child. Direct questions such as 'has anyone touched your tuppence?' will be necessary. Long interviews must be avoided, and time spent gaining a child's confidence is more productive than repetitive and exhausting cross questioning.

Common sense dictates that the child should be allowed to describe in detail what has happened in their own way, but to help the child it is necessary to reassure the child constantly that they have not done wrong, that it is right to tell, and that you will help them with the consequences of disclosure. The methods of communication will vary according to the child's developmental level and skills. Verbal disclosure may be too difficult for some children who have been told to keep quiet. Other methods include the use of anatomically correct dolls, ordinary dolls, drawing, or direct demonstration by the child using their own or someone else's body. There are no firm rules about the use of any of these materials and flexibility of approach is the key to success Children use a wide, and sometimes comical, sexual vocabulary and it is important to check what this is and to use it oneself in talking with the child.

Disclosure may be made before, during, or after the examination and sometimes follows months or years after the event. Children may indicate they have a secret, cannot talk to you, or say 'I can't remember' or 'I was asleep'. It is important that this is noted and communicated in reports so that work can be done to help the child to disclose later.

Evidence is accumulating that fictitious reporting of sexual abuse by children is uncommon,[5 6] usually confined to disturbed adolescents, and that children cannot and do not fantasise about specific sexual activities. Children should, therefore, usually be believed.

## Medical examination[7 8]

The purposes of this are threefold:

1. To make a complete assessment of the child in terms of health, growth, and development, with special emphasis on emotional and behavioural aspects and problems which may or may not be directly linked with abuse.
2. To collect and record forensic evidence of the abuse.
3. To treat the child—this must be incorporated at every stage.

It is assumed that paediatricians will be experienced in the assessment of the whole child, as in other types of abuse, and the discussion will be limited to a consideration of the forensic and therapeutic aspects.

### GENERAL POINTS

1. Abnormalities of the anus are found in 40 to 50% of boys and girls, and in 50 to 60% of girls there are vulval abnormalities.
2. Note the child's demeanour during the examination Is he or she angry, passive, cooperative, or frightened? Many children will be unexpectedly cooperative.
3. Older children may refuse to be examined and they should be given the chance to return later when they have had time to think about things. It is never justifiable to force a child to be examined. Anaesthetics or sedation are occasionally used to examine children who would like to be examined but who cannot relax, or where there are injuries which need surgical attention (in our experience this is uncommon).
4. The use of an auroscope, or simple illuminated magnifier, for examination of the vulva is useful. We note the use of the colposcope to improve the recognition of hymenal scars and tears, with perhaps a 10% improvement in diagnostic rate.[9] We feel the colposcope is of fairly limited use in diagnosis.
5. Photography is extremely useful. Our hospital photography departments have been very helpful, but one of us (CJH) uses a Nikon F301 camera with 105 mm F2·8 medical micro Nikkor lens and

SB15 flash unit to record findings. We would caution the use of photographs alone when a further medical opinion is requested, especially where photographs are not of good quality or do not record the dynamic signs.

Specific aspects include the following:

1 Examination for injuries, such as bruises, bites, and love bites or burns; the site of injury—for example, around genitalia, thighs, lower abdomen, and groins; grip marks, which may occasionally be seen on upper arms and knees; and bruising or redness of the perineum.
2 Genitalia should be examined carefully. In boys the penis and testes are uncommon sites for injuries, and these have been recorded in only 1% of boys seen. Tears of the foreskin frenulum are occasionally found. In girls the breasts (in older children) may show signs of injury and bites; there may be labial reddening and bruising with extension to perineum; the vulva may show abrasions, tears, bruises, and oedema. There may also be tears of the posterior fourchette and hymen, and the shape and size of the hymenal opening should be recorded. Under 6 years of age full penile penetration of the vagina is unusual and results in tears of the vagina. Dilatation of the hymen (in prepubertal children more than 0·5 cm is a rough guide) may have occurred. Digital assessment of girls after puberty should be made; if intercourse has taken place regularly two fingers may usually be inserted with ease. The anus should be examined with the child in the lateral position and buttocks gently parted. We do not routinely undertake digital or instrumental examination of anus and rectum. Examination of the anus is important,[10] because one third of abused girls and two thirds of abused boys have signs here. There may be reddening and bruising around the anus and loss of the normal fold pattern. Tears are commonly multiple or, if single, posterior. Measure the length and note the position. There may also be dilated veins, either in a complete ring or just an arc, and swelling of the margin of the anus, as well as scars and skin tags. There may also be dilatation of the anus and reflex dilatation on minimal skin traction to the buttocks, and twitching.
3 Signs of oral, pharyngeal, vaginal, and anal infection should be sought. In young children small nasopharyngeal swabs are useful, and one should establish with the laboratory which specimens they need to screen for gonorrhoea, chlamydia, and trichomonas. Children find it uncomfortable having these specimens taken so the swabs should be dampened under the tap first: it may only be possible to do two swabs together.

Specific forensic evidence for example, cotton wool swabs, again moistened with tap water—should be taken from skin, mouth, vagina, and anus and tested for spermatazoa and acid phosphatase, which are markers for semen. These swabs must be labelled and handed to a police officer who will send them for analysis. Forensic tests are most useful if done within 48 hours of the last contact, but most physicians working with abused children have noted that they are rarely helpful.

EXPLANATION

Throughout the examination, which begins with a general physical examination, it is important to explain every step and to reassure the child that he or she will be fine and that the symptoms will go. Children are beginning to ask about the possibility of acquiring AIDS and the need for serological testing is likely to increase. Other worries concern pregnancy and 'damage', which they fear may be lifelong. To some girls and families to hear, 'the hymen in intact', is extremely helpful. Many boys fear themselves to be homosexual and this can be dispelled.

The child needs to be told that the adult is entirely responsible for the abuse and that he or she is absolved from any blame or guilt. They need to know that they have been believed and that they will be helped. Finally, they need to know that they have acted correctly by disclosing the abuse and by allowing examination, the emphasis being on the child granting permission and thereby having control over his or her own body. All this should be reinforced with the parents.

## The nature of evidence in sexual abuse

Unlike physical abuse where much of the evidence lies in the injuries and the parents' explanations, in sexual abuse physical evidence may or may not be present and the degree of certainty that may be attached to it may vary. Gross evidence—for example multiple anal tears, reflex dilatation, and dilated veins—may indicate that penetration has taken place and that, in the absence of any other reasonable explanation, sexual abuse has occurred.

Lesser physical evidence is said to be consistent with the allegation of abuse in the statement from the child. Absence of signs is normal in oral abuse or masturbatory activity of the adult by the child, but this clearly does not mean that the child has fabricated the story. Also, as the law stands at present, a clearly given history by a young child (too young to be sworn or affirmed) is inadequate for a prosecution without corroboration.

The dynamic changes in the physical signs caused by time have not yet been reported, but it is clear that an abnormal anus can return to normal within days, weeks, or months. Follow up examinations are justified and essential to document changes and to distinguish normal anatomical variants or disease from the signs of abuse.

When addressing the mode of transmission of sexually transmitted diseases in children, one is aware of the occasional occurrence of non-sexual transmission. We would say that transmission of gonorrhoea has been by sexual contact—that is, sexual abuse, until proved otherwise. For other infections (herpes simplex type 2, *Trichomonas vaginalis*, venereal warts, and chlamydia) the evidence points to sexual contact being the usual form of transmission and their presence probably indicates sexual abuse. This subject has been well reviewed.[1]

### Therapeutic aspects of the paediatric role

Efforts to intervene effectively on behalf of sexually abused children and to reduce the emotional damage associated with this form of abuse should be incorporated at every stage. Many children have recalled the process of questioning and examination as damaging experiences. This can be overcome by an approach which is responsive to the child's needs. The issue of the sex of the examiner is less important than the sensitivity afforded to the child, but a woman doctor should ideally be available for those children who prefer and request one. Early counselling may be undertaken by the paediatrician who is in a good position to ensure follow up and help for the child and family.

### Talking to parents

Abuse perpetrated within the family has special difficulties. The perpetrator may have been named clearly by the child and immediate steps to separate the child from the perpetrator must be taken while further investigation ensues. In other circumstances, when the identity of the perpetrator is not clear, it is probably better to indicate to the parents that there is evidence of sexual abuse and that the child needs protection. A statement that everyone in contact with the child is necessarily under suspicion and that a police investigation is necessary sometimes encourages a reasonable response from the family, although denial of abuse is common. When the abuse is brought out into the open, either by disclosure or by professional intervention, is a dangerous time for the child, and we have repeatedly found that protection cannot reliably be left to the child's mother.

Admission to hospital can be an option while investigation and further talking to the child continues, but access of the perpetrator to the child may continue and ensure that the child remains silent. Immediate admission to a foster home or children's home is an alternative while investigation proceeds, with supervised access to the child. Siblings and other children in close contact should also be seen and examined in every case. It is unusual for abuse to be limited to one child in a family and common for all the children to have been abused.

### Reports and responsibility of other agencies

In this country responsibility under the law for the protection of children rests with the social service departments in each area, the National Society for the Prevention of Cruelty to Children, and with the police. All are empowered to take immediate and continuing responsibility for children thought to be at risk. The police also have the responsibility to prevent and detect crime and maintain the rule of law.

Every investigation should involve the police and one of the two child protection agencies. Where a diagnosis is clear, immediate referral to both agencies is the next step for the paediatrician, remembering the need to safeguard other children who may be, or have been, in contact with the perpetrator. Where the diagnosis is uncertain, the paediatrician may have to assess carefully, preferably in informal discussions with the police and social workers, how best to proceed. Increasing cooperation and confidence among agencies, hopefully through joint consultation and working, should foster earlier communication and discussion between people who trust one another to avoid precipitate, hasty, or unwise action on the one hand, or inappropriate delay or inactivity which leaves the child at continuing risk on the other.

A medical report should be written for use by social services. This may contain the sort of information which will be useful in the juvenile court, but a different report in the form of a statement should be written for the police. Police statements should list the symptoms and details of the physical condition as well as the allegations the child has made and whether the physical symptoms are consistent with the child's story. It is important that the doctor expresses an opinion. We find the phrase 'consistent with' is usually appropriate. It is important to keep the family doctor, as well as the other agencies, in touch with what is going on.

Evidence given in court, and also the expertise and professional standing of the paediatrician as a witness, will be cross-examined. The evidence should be given in a way which leaves the court to decide whether the child has been abused. Sexual abuse is what the law says it is; the best approach is to say that the history and examination are consistent with sexual abuse and be prepared to discuss what else they may be consistent with. There are usually few other relevant options, but defence lawyers will raise them. Other doctors may be available to challenge the findings, and it is reasonable to point out to the court that this difficulty is well recognised in these cases.

## Case conferences

Case conferences are called following diagnosis but, as long as protective action has been taken, their timing will depend on discussion between agencies The tasks are broadly similar to those facing case conferences for physical abuse, and children may be registered under the separate category of sexual abuse We believe doctors should provide both written and verbal evidence to the conference when practically possible.

## Treatment for child and family

There are no simple rules as to which child or family will benefit from help The paediatrician, in conjunction with other agencies, shares responsibility for ensuring that adequate help is offered in the form of individual, group, family, or part family therapy, as appropriate. This work is undertaken by social workers and also within departments of child psychology and psychiatry. The difficulties encountered in treatment are such that a structural multidisciplinary approach, backed by statutory legal measures in some cases, is essential. We have found that there is no place for 'going it alone', although families may wish to encourage doctors not to pass on information to other agencies; we would discourage adopting that approach. Making the vital link from the paediatrician to the helper can be made easier by close working and joint clinics. One of us has experience of working in a family treatment group and the other does a joint clinic with a child psychiatrist. Further follow up visits by a paediatrician are not required in most cases, but children and families should always be encouraged to return to discuss further worries.

Professional needs for support for the people working in this area are met in Leeds by the team approach. and we would suggest that paediatricians do not attempt to tackle this problem alone. Ideally, having two paediatricians, who can call on one another for second opinions and discussion, is recommended. Our team includes social workers and a psychologist who is trained in psychotherapy. Regular monthly meetings with the others working intensively in child sexual abuse have proved valuable.

## Conclusion

There is increasing evidence of the initial and long term harmful effects on children of sexual abuse.[12] On a global scale the scope of widespread abuse, neglect, and exploitation of children is being acknowledged.[13] Those who are prepared to work on behalf of children will need to be backed up strongly at a personal as well as professional level.[14] Sexual abuse is the abuse of adult power. Not only does the professional need to confront the results of this abuse for the sake of the child, but also on behalf of the power structures in society, the family, and the law, which so often fail to protect and care for children. This personal view sets out our initial conclusions in a new and rapidly expanding field. Everybody who involves themselves in this problem will have to resolve these and many other issues to their own satisfaction.

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# What to ask when sexual abuse is suspected

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Over the past few years there has been a considerable increase in the recognition and reporting of the sexual abuse of children.[1 2] Although the child often reveals the abuse to an adult such as a parent or teacher physicians who provide medical care to children (including paediatricians and general practitioners) are often the first professionals to suspect that abuse has occurred. Much has been written about the possible presentations of sexually abused children from vaginal discharge to symptoms less obviously related to sexual abuse such as abdominal pain, encopresis, or running away from home.[3 4] There are an increasing number of reports of the variety of physical findings[5-8] and on the appropriate laboratory investigations.[5 9 10] Despite this increase in attention to the problem, however, little has been written about how the physician should raise the possible diagnosis of sexual abuse with either the parent or child.

## Raising the possibility of sexual abuse

In a doctor's surgery concern about sexual abuse can be raised in two different ways. Firstly, the parent (usually the mother) or occasionally an older child or adolescent raises the issue with the doctor. The parent is seeking help to discover what has happened and to protect the child For example, a mother may mention that she is worried about sexual abuse because last week her 7 year old daughter said that her uncle 'had been rude with her.' The mother does not think that her daughter is making this up, but cannot be sure. By raising the issue she is giving implicit permission for the doctor to talk to the child about the event and carry out an appropriate medical examination.

By contrast, the issue can be raised if the doctor, during the evaluation of the child, becomes suspicious about the possibility of sexual abuse In such circumstances he will be faced with several questions Could the child have been sexually abused, or could there be some other explanation for his findings? What is the best way to raise the issue with the parent(s) and child, keeping in mind that the parents might be offended and angry? If direct questions are asked and the child denies that anything has happened, has the diagnosis of sexual abuse been excluded? How much questioning is necessary before being reasonably certain that nothing has happened (given that it may be impossible to exclude completely such a diagnosis)?

There are at least three different circumstances when there is no direct allegation but when the doctor may consider the diagnosis of sexual abuse and have to ask questions of the parent and child. These are:

(i) when a child has a complaint that might be directly related to the possibility of sexual abuse, such as a girl with a vaginal discharge;

(ii) when a child has a complaint that is not directly related to the possibility of sexual abuse, such as abdominal pain or encopresis;

(iii) when a child has no complaint but an incidental finding, such as an enlarged hymenal ring, makes the doctor suspicious.

### A COMPLAINT RELATED TO THE POSSIBILITY OF SEXUAL ABUSE

The first is perhaps the easiest occasion on which to raise the question of sexual abuse. Direct questions may be part of the history taking before examining the child: 'Do you have any idea how your daughter got this vaginal discharge?' 'Could anyone have touched her in the vaginal area where she is having this problem?' When a preadolescent child is being examined with the mother in the room, it might be appropriate to ask the mother's permission to talk to the child· 'I'd like to ask your daughter some questions about the same topic, as well.' During the examination of the child's vulva, the doctor might ask, 'What do you call this part of your body? What comes from there?' If the child has difficulty answering, the mother may be asked what the family calls that part of the body. The doctor may then ask about touching: 'Has anyone touched you there?' If the child denies that anyone has touched her, the doctor may ask about who helps her in the bath: 'Who washes you there? Do you wash yourself there now or does someone help you?' 'Does anyone ever put ointments or medications there?' 'Does anyone else ever touch you there?' Watching the way that the mother or child responds may be as helpful as the actual responses to the questions. For example, the doctor may be less concerned about the possibility of sexual abuse if the child seems relaxed for the setting and answers questions appropriately (this may include embarrassment or amusement, or both, at the questions about names of parts of the body or amazement at questions about who touches her private parts). In contrast, more worrying kinds of responses might include obvious changes in mood after specific questions (such as looking sad, frightened, or 'frozen'), more difficulties than expected for age in answering certain questions; or a string of 'No' responses that seem to shut out the interviewer or to be overinsistent denials rather than statements that nothing has happened.

At this point, experts in interviewing young children suspected of being sexually abused, might try a more indirect approach by using hypothetical questions to find out if abuse has occurred [11] Although we described this technique, we believe that it should be used sparingly if at all, except by experts, because of the difficulty in interpreting the child's responses. Examples of such questions (to the mother) would be; 'If someone had touched her there, who would she tell?' and to the girl, 'If someone had touched you, who would you tell?' 'If you were touched, would it be a nice touch or a rude touch?' 'Would it have hurt a lot or a little?' 'Would it be more rude if you were touched by someone who was not part of your family or was in your family, like your father, sister, or brother?' This style of questioning may be helpful when asking about difficult or sensitive topics when it may be considerably more difficult for the child to say what has happened than to deny it By not asking direct questions, the child has the opportunity to indicate what he or she may do (or have done) For instance, a child who has been abused may respond with more details than would be expected for a child of that age who has not been abused, who might say that she doesn't really know whether it would hurt 'a lot or a little.'

Finally, a few direct questions may help the child to indicate what has happened. 'Has anyone touched you there?' 'Does your daddy or your sister or your brother ever touch you there?' Of course, it is important to know who is in the family and household and who else looks after the child.

If the answers to such questions do not raise concern about the possibility of sexual abuse and if the medical examination is negative it would be reasonable to assume that the child has not been abused. If, however, either the responses or the medical examination raise concern, then arrangements should be made for a case conference to be convened and for the child to be interviewed more extensively by a clinician with special expertise in the diagnosis and treatment of sexual abuse. If the parent asks why you are concerned about sexual abuse, it is easy to explain that because of all the recent publicity about the problem, it is medically indicated to ask such questions.

### A COMPLAINT NOT DIRECTLY RELATED TO THE POSSIBILITY OF SEXUAL ABUSE

Under these circumstances the doctor may be asked to evaluate a child with a psychosomatic complaint such as abdominal pain, anorexia, or a psychiatric symptom such as attempted suicide. After taking a complete history and examining the child it may be appropriate to interview him or her alone. How should one go about introducing the topic of sexual abuse? During the interview the doctor may explain that sometimes problems like the one that the child has are not due to physical abnormalities, but rather to tensions or worries, particularly secret ones, and that there are lots of kinds of worries that children have that may cause such symptoms. After this kind of statement the doctor may mention various kinds of worries and secrets including the possibility that someone has been abusing the child

Of course, the extent of the exploration would depend on the results of the examination so far. If it is clear from the history that the abdominal pain is due to recent identifiable stresses in the child's life, such as difficulties at school or parental discord, then one would be less likely to explore extensively the possibility of sexual abuse. On the other hand, if the cause of the symptom is not clear, then it would be reasonable to spend a portion of the interview asking about sexual abuse: 'Sometimes children like you who are having difficulties with soiling have been hurt or touched in a bad way on the bottom; could that ever have happened to you?' Or, 'Sometimes children who have pain like yours are worried because someone has been touching them in a way that they don't like, but they don't know how to stop it or who to tell about it. Has that been happening to you?' 'Even if it has happened, most children find it very difficult to talk about. Have you been worried about that?' Because it is often difficult for the child both to talk about the abuse (if it has happened) and to find the right words to describe the events, a denial should be considered in the same way as denials about other painful topics; the questions may have to be repeated in future, and the doctor should be willing to listen to the child if he or she makes oblique references to the topic.

A SUSPICION OF SEXUAL ABUSE BASED ON A ROUTINE PHYSICAL EXAMINATION

The most difficult situation occurs when an abnormality is detected on a routine examination that raises the possibility of sexual abuse That the child and parent have not come to the doctor with a specific complaint makes the situation especially difficult. There is always the temptation to ignore or belittle the finding and not to mention it, as might occur after detecting a soft heart murmur and not mentioning it to save the parents from worrying. A more reasonable approach, especially if one is uncertain about the abnormality, is to refer the child to a doctor with experience in examining sexually abused children In discussing the physical finding, a direct approach often works best: 'I've noticed what looks like an abnormality at the opening of your child's vagina. I'm not 100% sure, but I think there is some scar tissue there. Do you know if anyone has been touching or hurting your daughter down there? I may need to do some further investigations. I would like to talk to your daughter for a few minutes alone, and then I think that it would be best if she was examined by someone with more expertise than me.' The types of questions to the child that follow would be similar to those presented above.

## The interview with the child and further action

Because the child and parent have ostensibly come to the doctor for an evaluation of a physical problem or for a check up, the questions about the possibility of sexual abuse should be asked with care and after a rapport has been established. Although it is not unreasonable to ask the child questions with the parent in the room, there may be times when the child may not be able to say what has happened in the adult's presence The child may be worried that his mother might blame him for what happened, or he may be worried because the parent in the room is the abuser. If the child seems hesitant in the parent's presence or if the parent always answers for the child, it may be helpful to see the child alone for a few minutes. Children who are at least 6 or 7 years old might be seen alone from the beginning of the interview.

There are times when it is better not to ask further questions. A child may become so upset that it would be wise to stop the interview and indicate to the child that she appears very upset by the questions and that it is difficult to talk about such topics. To make clear to the child that the doctor recognises her pain, it may be helpful to add, 'I'm worried that you were touched in a way that may have been rude, and I would like to arrange for you to talk to someone else about what happened.' In such a case an inpatient evaluation may be helpful, and this should be dicussed with the parent before mentioning it to the child.

In some circumstances the gender of the doctor may influence whether the child feels comfortable enough to be able to answer questions about the abuse As most offenders are male, there may be times when a male doctor may be more successful interviewing a child in the presence of a female colleague; likewise, pairing a female doctor with a male colleague may sometimes be helpful.

RAISING THE POSSIBILITY OF SEXUAL ABUSE

The initial question about the possibility of sexual abuse is more difficult to ask in theory than in reality. Although parents may be surprised, alarmed, or angered, they have certainly heard about such problems and do not find the question unreasonable. The major difficulty for the doctor is then to know when a denial, particularly by a child, truly indicates that nothing has happened as opposed to a false statement because of previous threats or worries about revealing the secret.[12] As in the assessment of other clinical problems, the information provided by the child has to be amalgamated with other data, including the child's behavioural symptoms (the teacher reports that the child has been repeatedly touching other children in the genital region); the medical history (recurrent episodes of vaginal discharge), the family history; the physical examination; and the laboratory investigations. If the hymenal ring looks slightly enlarged, but the remainder of the data do not give cause for concern, it may be best to re-examine the child in several months and in the meantime assume that the child has not been abused. On the other hand, if *Neisseria gonorrhoeae* is cultured from a vaginal discharge sexual abuse has occurred regardless of any statement that nothing has happened.

In proceeding with the initial evaluation, the physician should be prepared to make several important decisions:

WHO SHOULD BE TOLD ABOUT THE SUSPICION OF SEXUAL ABUSE?

*Telling the parent*

If information from the interview or physical examination indicates that the child has been sexually abused, it is best to inform the parent of the findings. If, however, the doctor is concerned about the possibility of sexual abuse but cannot make a clinical diagnosis then he or she has to decide how much to tell the parent. Usually the doctor outlines the concerns and the recommendations for further evaluation; on rare occasions, however, it would not be in the child's best interests to indicate the specific concerns[13] For example if the doctor is worried that the accompanying parent is involved in the abuse, he might withhold the details from the parent for fear that he or she may pressure the child not to talk further. Under such circumstances, the doctor may say: 'Your daughter appears to have some worries, and I'd like to arrange for her to talk with someone in more detail about these.'

*Informing the social services department*

In the United States the laws of each state require that the doctor report cases of suspected sexual abuse, not just confirmed cases, to the state's protective service agency. In the United Kingdom reporting of child maltreatment is not compulsory. The guidelines, *Child abuse—working together*, from the Department of Health and Social Security, however,[14] recommend that cases of suspected sexual abuse should be reported to the local social services department or the National Society for the Prevention of Cruelty to Children (NSPCC), and through these agencies to the police so that there can be a thorough investigation of the allegation. Without such a referral it is usually impossible to carry out an adequate evaluation or to ensure protection of the child. As part of this evaluation the social services, the NSPCC, or the police may ask for assistance from a variety of specialists (paediatrician, police surgeon, child psychiatrist, child psychologist, and so on). At some time, either during the initial investigation or shortly thereafter, a case conference should be held, and the findings discussed by all who have been involved in the investigation and who have responsibility for providing services to the child and family.

#### IF SEXUAL ABUSE IS SUSPECTED, SHOULD THE CHILD BE ALLOWED TO GO HOME?

The decision to allow a child to go home should be made jointly with the social worker (sometimes only after an initial case conference) and will depend on the certainty of the diagnosis, the safety of the current living arrangements, and the ability of the parent to protect the child. For instance, if there is a strong suspicion that abuse has occurred from the child's evidence alone, but the mother seems to believe her child and understand the concerns, and if the child will not be living with the alleged perpetrator until the matter is resolved, then it seems appropriate to allow the child to go home. There are, however, three risks to allowing a child who is being abused to return home. The child may be threatened and told not to say anything else about the abuse, subsequently retracting her or his statement; the child may continue to be sexually abused; or the child may be physically abused for revealing the secret. Obviously, all three of these possibilities are highly dangerous for the child. If the doctors decide that it is not safe for the child to return home he or she may stay with a relative, be placed in an emergency foster home, or be admitted to hospital until a more appropriate arrangement can be made. If the parents disagree with placing the child away from home, social services may need to take emergency legal action (in the United Kingdom a place of safety order, or in the United States an order of temporary custody) and arrange temporary accommodation to ensure the child's safety

#### SHOULD THE ALLEGED PERPETRATOR BE INTERVIEWED AS WELL BY THE PHYSICIAN?

When an accusation is made about a person, he or she is usually interviewed by a police officer (sometimes accompanied by a social worker). Representatives from the police and social services departments have the statutory duty to investigate cases of suspected sexual abuse.[14] Occasionally the alleged perpetrator may want to speak to the doctor who made the initial evaluation. In such circumstances it is helpful for the doctor to consult the police and social services about when best to conduct the interview

Doctors who are experts in the management of cases of abuse and sexual abuse may participate in joint interviews with social services not only to clarify the medical findings, but also to explore possible ways in which abuse may have occurred. These are often difficult interviews: the alleged perpetrator may be angry or threatening, or he may be convincing in his statements of affection for the child and denial of sexual abuse. In these latter circumstances the professionals may wonder whether the information from the child's interview or physical examination was overinterpreted or misunderstood.

#### SHOULD THE SIBLINGS BE INVESTIGATED?

Because siblings may have been sexually abused as well, examinations of these children should be arranged as soon as possible. Social services may arrange these and ask that the physician examine the siblings for signs of physical and sexual abuse.

### Do children lie about the occurrence of sexual abuse?

Often the diagnosis of sexual abuse is clear, but sometimes it is difficult to sort out exactly what happened to the child. It is in these circumstances that it is important for the doctor to believe what the child says and help to protect him or her during the initial stages of the evaluation. There are, however, occasions when it is best to be cautious about the diagnosis, although most experts feel that these occasions are rare.

Suspicions that are based on the history may turn out to be unfounded because either a thorough evaluation fails to confirm the suspicion or the specific allegation by an adult or child is found to be fictitious. An example of the first type of case is an evaluation that finds no evidence of sexual abuse in a 3 year old child who is referred because of unusual sexual play in a nursery school. An example of the second type of case is an evaluation that finds no evidence of sexual abuse in a 5 year old who has alleged to have been abused on an access visit by his natural father. These cases may include lies, as well as misunderstandings or confused interpretations of the behaviour of others.[15]

Only a few reports have investigated the incidence of either type of unfounded accusation. In one study doctors found no evidence of sexual abuse in 4 of 64 children (6%) aged from 2 to 12 years who were evaluated for suspected sexual abuse for six months in the casualty department of a large urban hospital in 1975.[15] In a more recent study the senior author reviewed the records of 83 consecutive children all less than 7 years old who were referred to a hospital for suspected sexual abuse.[17] In 14% there was no evidence of sexual abuse; these children often were either very young (less than 3 years old) so it was difficult to obtain information from the interviews, or were siblings of sexually abused children. Jones *et al* reviewed cases that were referred to a local child protection agency: of 439 referrals with adequate information to permit an independent review, 22% were considered to be unsubstantiated.[15] This figure is likely to be higher than that seen at a hospital because the agency received referrals from a variety of sources including 'neighbours, relatives, child minders, and professionals.'[15]

As part of the same study, the authors examined the incidence of fictitious allegations. Of the 439 referrals to the local child protection agency, 34 (8%) were classified by the investigators as fictitious, 26 by adults (6% of all the cases) and eight by children (2%). Fictitious allegations were noted even more infrequently at the regional child abuse centre, the Kempe Center at the University of Colorado. From 1983 to 1985 there were 21 cases (3% of 717) compared with 696 cases of convincing accounts (no mention is made of cases that were not substantiated). Of these 21 accounts, five were made by children, nine by adults, and seven by both. In the five cases in which a child made the allegation, four of the children had been sexually abused in the past and were suffering from an untreated post traumatic stress disorder. In the cases in which an adult made the allegation, all were women, six had been abused, neglected, or deprived or both in the past, and five had considerable emotional disturbances; in seven of the cases, there also was a custody or visitation dispute. Finally, all the cases in which the allegation came from both the child and adult involved 'bitter' custody or visitation disputes; in addition, all the mothers concerned were psychiatrically disturbed, three of them having been sexually abused at about the same age as the index child.

Thus fictitious allegations of sexual abuse are sometimes made, although rarely by children. When such allegations are made there are often unusual circumstances. More commonly occurring cases seem to be those in which the suspicion of sexual abuse is not substantiated. As professionals become more vigilant about the manifestations of sexual abuse, the incidence of these unsubstantiated cases may increase because children with milder and more non-specific symptoms will be referred for evaluation.

Experts on interviewing young children about sexual abuse have discussed approaches to distinguishing true allegations from fictitious ones.[18 19] Important factors are the child's attitude when telling them about what happened, the description of the details of the events (including the sexual actions, whether the child was hurt, who was present, and where the events occurred), the description of any threats to maintain secrecy, and the response to telling the doctor. Other reports have noted that it is particularly difficult to assess the accuracy of an allegation when parents are fighting over custody of the child.[20 21] In such circumstances one parent may be convinced that abuse has occurred and distort the child's memories of contact to induce the child to accuse the other parent of sexual abuse. The occurrence of fictitious allegations is much higher in these cases than in other clinical presentations.[20 21]

If the diagnosis of sexual abuse is to be made, doctors who care for children should be aware not only of the presenting symptoms and signs, but also of how to ask about the possibility of sexual abuse, how to listen to the child's responses, how to integrate the preliminary findings, and how to make referrals to the appropriate child protection agency. While it is true that making the diagnosis of sexual abuse can have tremendous implications for the child and family, not making the diagnosis can leave a child in a dangerous situation of continuing abuse.

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## Commentary

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Much of what Hobbs and Wynne say is uncontroversial and merely describes in detail the accepted practice succinctly laid down in the current Department of Health and Social Security (DHSS) guidelines for dealing with child sexual abuse—a multidisciplinary investigation should take place and the child should be talked to and examined in a sensitive manner in a clinical setting. It is the specific aspects of the medical examination and the conclusions that they draw which are extremely controversial: they state that 40% to 50% of boys and girls have anal abnormalities.

Four women doctors in the Greater Manchester area doing examinations at the request of police, social workers, the National Society for the Prevention of Cruelty to Children (NSPCC), and paediatricians saw approximately 500 children in 1986 (Robinson, Jacobs and Welliver, personal communication). They always take a full history and talk to the child and carer about medical problems as well as any history of abuse. A history of possible anal interference is obtained from a much smaller proportion of these children than from the cases reported by Hobbs and Wynne, and in only a handful has definite medical evidence in the anal area been found. Precise figures are not yet available but they are in the process of being prepared for publication. Police surgeons throughout the country have made the same observations and the subject was exhaustively discussed at the recent Association of Police Surgeons of Great Britain annual meeting. None of the experienced police surgeons, many of them having the Diploma in Medical Jurisprudence and most of them experienced general practitioners with considerable experience of children, has found anything more than an extremely small proportion of children with anal evidence of sexual abuse.

Hobbs and Wynne say that they can tell merely by inspecting an anus that it is lax. They use the subjective and misleading test of so called 'reflex dilatation' on skin traction on the buttocks to make a definitive diagnosis of 'sexual abuse.' The opening of the anus on inspection—which should be done without traction by gently placing the hands on the cheeks of the buttocks—is variable, misleading, and present in a number of other conditions including chronic constipation, thread-worms, and anal thrush following courses of antibiotics.[1] Even if it is present in some sexually abused children (and more than half of them have no abnormal medical findings) it cannot be used as evidence (except as possible support to other relevant evidence) because it is also present in some children with other diseases who have not been abused. The same considerations apply precisely to anal twitchiness and dilated veins.

A few years ago I believed that flattening of the labia around the vaginal opening was a good sign of persistent attempted penile penetration, but I am now much more cautious in interpreting this sign because it can occur as part of normal development (and for other reasons) and is not reliable enough as a sign of abuse per se, even though it may have been caused by abuse. The anal findings described by Hobbs and Wynne are subject to the same reservations and much more caution is needed in their interpretation than has been demonstrated hitherto.

The vaginal findings in girls can be difficult to interpret. Cantwell's paper, on which Hobbs and Wynne base their opinion (that 0·5 cm is the accepted upper limit of normal for the size of the hymen), is open to many criticisms.[2] After the child's hymen was measured (inaccurately) by placing a tape or ruler against the vulva, leading questions were asked of the child. Even after this quite unacceptable practice only 74% of the children with larger openings were diagnosed as having been sexually abused. Is the size to be the same for a babe in arms and a big girl of 11 or 12? There is considerable risk that when paediatricians (and other doctors) look at a child's genitalia they will mistake the vestibule for the hymen and erroneously state that the vaginal opening is too large. A recent paper reported that only 59·1% of doctors including paediatricians correctly indentified the hymen on a colour photograph.[3] Errors are easy to make when there is a congenital frilly hymen that may be mistaken for tears, and where the doctor's knowledge of anatomy and pathology is inadequate; 'heaped-up scars' of the hymen have been described.

Reddening and bruising around the anus and vagina are of importance where there has been recent traumatic interference but there is great danger in paediatricians with no forensic training and no experience of the ageing of bruises and other injuries giving opinions as to the likely cause of such findings. Hobbs and Wynne give no evidence that they know the proper techniques for determining that a discolouration is a bruise, and not, for instance, a birth mark; Reid has emphasised the pitfalls for paediatricians in this area.[4] When giving evidence in court a doctor who has examined a child must be able to give an opinion as to what may have been the cause of the findings, how many times it has occurred, what has been used and with what degree of force. It is not enough to say 'consistent with sexual abuse' without being able to say whether a penis has entered the anus or whether it is the tip of a finger. Case conferences and proceedings in juvenile courts for care orders have been satisfied with a much lower standard of evidence than that acceptable in a criminal case, but the consequences for the child and the family may be just as serious and damaging. We must therefore strive to improve the quality of the evidence at all levels and make sure that the diagnosis is based on sound medical and medicolegal principles.

Dr Leventhal gives useful advice about talking to children, but there is increasing concern among doctors and lawyers about the use of the techniques described. Used by a kindly, skilled, and experienced interviewer they can be helpful, but there is a serious danger of them being used inappropriately. 'How much questioning is necessary before being reasonably certain that nothing has happened (given that it may be impossible to exclude completely such a diagnosis?).' Many interviewers using these techniques seem to work on the basis that abuse has taken place and will never take 'no' for an answer. If the child denies abuse it is said to be 'blocking' and must continue to be interviewed until the 'blocking' is released. In my experience children find the repeated interviewing and continual reference to the same subject distressing or boring. Under continual pressure they can become confused and having learnt which answers appear to be acceptable may eventually give the answer sought.[5 6] Continued interviewing of the child can in some cases constitute an abuse in itself.

Both these papers, though containing much that is useful and helpful also contain dangerous and unfounded assumptions: the uncritical acceptance of these has already led to enormous difficulties for many people trying to help sexually abused children and not least for many children and their families.

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Drs Hobbs and Wynne comment:

Our paper sets out our own working practice evolved from study and experience in child abuse and we await the Department of Health and Social Security (DHSS) for guidelines which are not (as Dr Roberts implies) available yet We are pleased to note that our view that children should be seen away from police stations has not been challenged. The concept of paediatric as part of multidisciplinary assessment, follow up, and treatment—including referral to psychologists and psychiatrists with whom the doctors have clear working relationships—seems to have been accepted, implying a significant change in the practice of police surgeons.

We recognise, as does Dr Roberts, that anal abuse has not been diagnosed in large numbers of cases in the past either by police surgeons or paediatricians, but would remind Dr Roberts that in the past the majority of children being seen by police surgeons were older girls in whom vaginal abuse is relatively more common Police surgeons are already beginning to recognise more cases of anal abuse and the interest and discussions which followed the lecture given by one of us (JW) to the police surgeons' annual meeting underlined the acceptance, at least in part, by many of the police surgeons of the findings that we published in the *Lancet* in 1986 under the title· Buggery—a common syndrome of child abuse.

We expect that as more boys and younger children are carefully examined more cases of anal abuse will come to light The physical signs that we have described are not new and papers written by forensic physicians have quoted similar findings.[1-4] We hold by our view that reflex dilatation of the anus correlates highly with continuing abuse, disappears when children are removed into a protected environment, and is not found in diseases such as thrush, threadworms, or constipation We would hypothesise that this is a protective reflex which serves to minimise the forced trauma of anal penetration by reflex inhibition of the normal anal sphincter spasm which every doctor recognises when he attempts to do even a gentle digital examination of the rectum These abused children have learned that accommodation (relaxation) protects from injury and pain

We would, however, point out that it is usual to find other signs of anal damage in the form of fissures, veins, thickened perianal skin, scars, and other symptoms and signs of abuse, so that a diagnosis is never based on this alone.

We would agree that interpretation of genital signs in girls is difficult and controversial Cantwell's paper is nothing more than a guide but it remains to date the best piece of work available in an under-researched area of children's medicine where studies by police surgeons are even fewer than those by paediatricians The fact that 74% of children with 'larger openings' described sexual abuse is to our minds an extremely interesting finding and not one to be dismissed because the doctor approached the questioning in a way which encouraged the children to disclose their abuse

Dr Roberts is not clear what alternative she proposes on vaginal diameter, unless she is to include it in her forthcoming publication on her experience of the 500 children she and her colleagues saw in Manchester in 1986

Finally we would like to take up the point that Dr Roberts makes relating to as she puts it 'the lower standard of evidence in the juvenile court' Certainly the requirements of proof are different—beyond reasonable doubt as against balance of probability in the juvenile court—but there is little doubt that the evidence that the juvenile court hears including all the details of the child and family (with little excluded) must provide a far better and more complete picture of the abuse that the child has suffered than evidence available to the criminal court In criminal proceedings we are frequently told that we cannot relate what the child has told us to the court and that only physical findings can be discussed Social history and assessments are not included. Perhaps it is these imposed legal restrictions aimed to protect the accused that have so profoundly influenced the police surgeons thinking on this subject, and also ensured that the majority of abused children do not receive justice within the present legal system

In the current controversy, it is interesting to find some paediatricians in alliance with the powerless and the abused—that is the child—and some police surgeons in alliance with the more traditional authorities in the form of the parents and the police The *New Statesman* (31 July 1987), in a well researched analysis of the issues involved in the Cleveland controversy, underlines this point well

It is as much these differences in philosophy that prevent us moving closer to Dr Roberts' view, than merely the interpretation of the scientific material which is already available

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# Correspondence

## Prolonged exclusive breast feeding and heredity as determinants in infantile atopy

Sir,

The observation in the Finnish study that prolonged breast feeding is associated with a higher incidence of infantile atopy, heredity being its only reliable predictor, is not surprising and warrants some additional considerations[1] Dr David's commentary omits some of the basic biological aspects.

In many studies atopy is assessed by the onset during infancy of certain clinical signs possibly caused by atopy. Whether breast feeding can or cannot delay the onset of these signs is not the same question as whether or not atopic disease itself can be prevented. In a number of inherited metabolic disorders—phenylketonuria, for example—a suitable diet can prevent symptoms from developing, but cannot eliminate the underlying congenital disorder.

Furthermore, we are a long way from knowing whether and to what extent atopic signs and symptoms during infancy are antigen or host dependent From findings in animals and in cultured fetal intestinal tissues, various factors available in breast milk have been shown to stimulate the gut surface, possibly exaggerating the infant's immune responses, as recently reported by Raloff[2] In addition to heredity factors, breast feeding could even enhance the host's capability of eliciting a reaginic response with consequent earlier clinical presentation of atopy, an argument invoked to discourage the combination of breast and formula feeding.[2]

Some foods ingested by the mother pass into the milk and can sensitise the infant Also, various milk proteins from the mother may have immunogenic power due to the frequent occurrence of polymorphic variants genetically arranged in different structural forms They include the not strictly alimental milk proteins like immunoglobulins, blood group, and HLA specific glycoproteins and transferrin, and also specific milk proteins, like casein.[3] The traditional statement that mother's milk proteins are homologous for her infant is contradicted by the presence of allologous proteins which have potential immunogenic capacity when they come into contact with the immune system of an infant differing from the mother for that allotype.

It is not surprising that prolonged breast feeding may be associated with a higher incidence of infantile atopy when compared with limited breast feeding because of the more prolonged exposition to maternal allotypes and possibly because of its adjuvant effect in the sensitisation process.[1] The same explanation might apply to the observation that by witholding certain sensitising foods from the lactating mother's diet the incidence of atopic symptoms is lowered, but not avoided

These observations indicate the biological uniqueness of breast feeding that appears to be an exclusive way for the developing infant's immune system to be instructed and adapted to react through exposure to dietary antigens which, unlike all others, will never be encountered again in the course of life

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## Congenital dislocation of the hip: to screen or not to screen

Sir,

The personal experience of Mr Dwyer[1] confirms my view that most abnormal hips may be safely and effectively diagnosed and treated at birth.[2] The excellence of his results reflects credit on him and on his team including the physiotherapists who I understand do the primary screening in his hospital

In only one aspect does Mr Dwyer's practice differ appreciably from that recommended recently by the Standing Medical Advisory Committee and the Standing Nursing and Midwifery Advisory Committee.[3] The success of clinical screening in the neonatal period in his hospital seems to have suggested to him that follow up screening is not required beyond the age of three months. While this may be the case if screening is undertaken by 'a dedicated, experienced and skilful team', the availability of such support is difficult to achieve and maintain For this reason the SMAC/SNMAC guidelines stated that 'it is essential to reassess the possibility of this condition until a child is seen to be walking normally' Their report recommended that the hips of all children should be routinely surveyed not only at birth and on discharge from neonatal care, but also at 6 weeks, at 6–9 months, and between 15 and 21 months of age. This advice is surely sensible. Late cases of established congenital dislocation of the hip still occur even in the best centres and—as is well recognised—the later the diagnosis the more difficult the treatment and the more likely is the occurrence of avascular necrosis of the head of the femur.

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[3] Standing Medical Advisory Committee and Standing Nursing and Midwifery Advisory Committee Screening for the detection of congenital dislocation of the hip *Arch Dis Child* 1986,**61**:921–6

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## Liaison psychotherapy in a hospital paediatric diabetic clinic

Sir,

Drs Josse and Challoner's paper highlights the importance of liaison psychotherapy in the management of diabetes, an illness with recognised psychological components [1]

Our experience over the past seven years has suggested that a psychotherapist's skills are useful in a wide range of paediatric work. A member of the 'team' who is not involved in day to day management can define the psychological impact of illness, dying, and handicap on the child and his family and on those who care for him, and can help them.

In our hospitals, in addition to working with individual children and their families, the liaison psychotherapist holds two weekly staff groups for nurses. One group is in a specialised setting—a special care baby unit[2]—and the other is in a general paediatric ward The work of each group is aimed at augmenting the care of patients by helping the staff to find constructive means of working with the various amounts of stress present and to facilitate a greater understanding of the psychological aspects of child and family functioning by means of implementing this in treatment. A psychotherapeutic approach to liaison work needs not only a knowledge of family systems theory but also an understanding of the various dynamic forces at work in the psyche, for example, unconscious conflicts and anxieties and the association between these and child development and family functioning. His training in therapeutic techniques, both individual and family, can help provide paediatric staff with additional ways of working with patients and their families

An integral part of any team is the medical social worker who provides among other things a link with the community, necessary statutory work, and the tackling of multifarious social problems. Many social workers are skilled in the techniques of supportive counselling and family treatment and provide a valuable service Their work is complementary to the psychotherapist's whose lengthy specialised training enables him to work quickly at a depth which can bring about effective change.

Constructive paediatric psychotherapeutic liaison can only take place, however, if the psychotherapist is able to take a common sense aproach to working with medical staff It is necessary to find ways in which their skills can be practically used in paediatric work. This precludes the superimposition of metapsychological theories and their accompanying jargon, which are wholly impractical and understandably alienating in this field.

We feel that liaison paediatric psychotherapeutic work has much to offer the National Health Service and more effective training, including fieldwork, is required

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[2] Van Dias S Psychotherapy in special care baby units *Nursing Times* 1987,**83**:50–2.

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## Mercury as a health hazard

Sir,

Curtis *et al* reminded us that pink disease still occurs and mercury remains an occasional environmental hazard,[1] but were all their cases of pink disease due to mercury poisoning? Certainly this toxic metal causes the severe disease, but the similarity between mild disease and the appearance of some severely disadvantaged children with 'deprivation hands and feet' has been noted.[2] After reviewing reports of the disease it seems to me that the diagnosis of pink disease was often made on clinical grounds alone without laboratory confirmation. The condition was most frequent among the poorer sections of the community and many children responded to close follow up and support at out patient clinics, displaying weight curves that latterly would fit catch up growth where social circumstances have improved [3] Perhaps mild pink disease was simply a marker for social deprivation and unrelated to mercury poisoning?

Would senior paediatricians who manage the disease like to comment on this hypothesis?

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**References**

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[3] Calvert T The weight in pink disease *Arch Dis Child* 1955,**30**:524–8

# Establishment of an intermediate care ward for babies and mothers

Sir,

Dear and McLain have shown clearly how the establishment of an intermediate care ward reduced the admission rate to their neonatal unit Although such a ward may be useful in some hospitals, a similar admission rate has been achieved at this hospital by different means

In 1979 the admission rate to the neonatal unit was 15·7%. Seven years later it had fallen to 5·2% of babies delivered at the hospital. This was achieved by nursing all babies who fulfilled the criteria described by Dear and McLain for admission to their transitional ward on the postnatal wards Some babies weighing <1700 g were also nursed with their mothers on the postnatal wards, but all babies with respiratory distress or who required intravenous fluid replacement were admitted to the neonatal unit.

The policy of nursing babies with special needs on the postnatal wards was effected by allowing all midwives of staff nurse grade and those newly appointed as sisters to spend six month periods on rotation to the neonatal unit Thus expertise and familiarity with the problems of small babies were spread through the whole hospital.

This policy of rotating midwifery staff had two additional advantages Firstly, staff from the lying in wards were able to help out in the neonatal unit when required and, secondly, because all nursing staff had personal experience of the problems of the neonatal unit, this maternity hospital functioned as an integrated unit rather than the needs of special babies being separated from others.

**Reference**

[1] Dear PRF, McLain BI Establishment of an intermediate care ward for babies and mothers *Arch Dis Child* 1987,**62**:597–600

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# Preterm blood counts vary with sampling site

Sir,

Thurlbeck and McIntosh have recently studied the changes in neutrophil counts at different sampling sites [1] In their study, 0·5 ml of blood was drawn through an umbilical artery catheter, and then 0 5 ml was obtained by free flowing heel prick (n=10) or peripheral venepuncture (n=21). The average difference between the capillary compared with the arterial neutrophil counts was +1800 cells/mm The difference in neutrophil counts between venous and arterial blood samples was not significant They therefore concluded that it is important to sample from a vein or artery, rather than a capillary vessel, to avoid error in interpretation

The cause for the increased neutrophil count in capillary blood is not clear from this study One important possibility is that a rise in the blood neutrophil count during the prolonged capillary sampling may occur, induced by the pain it causes This may also explain the higher variability found in the neutrophil counts in capillary blood

A significant rise in white cell count from the marginal granulocyte pool may follow exercise or injection of epinephrine, and occurs with remarkable speed [2] Counts of 35 000 cells/mm have been recorded after a 400 m run completed in one minute.

We have recently studied the white cell count in venous blood before and 10 minutes after lumbar puncture in 20 neonates. There was a significant (p<0 001) increase in the white cell count from a mean (SD) of 9·6 (3 4)$\times 10^9$/l before, to 13·4 (3 7)$\times 10^9$/l after the procedure, caused by a rise in the neutrophils and lymphocytes There is a reason to believe, therefore, that the higher neutrophil counts found in the samples from capillary blood were associated with the order of sampling used in the study and not necessarily with the site itself.[1] If that is the case, venous and arterial sites will also fail to give reliable counts if samples are taken during or after stressful events This question could have been answered if a third blood sample had been taken through the umbilical artery catheter after the capillary sampling, or if the order of sampling had been randomised

**References**

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Dr Thurlbeck comments.

Dr Shohat's interesting letter raises points which would have been discussed more fully had space allowed. Arterial sampling, which does not disturb the infant, was performed first because of the effect of painful procedures on the neutrophil count in term infants which has already been described.[1] This could well be a reason for the difference which we observed but it is of note that venous sampling, which is presumably painful too, had no effect. It is inaccurate to describe the observed difference as being due to the order of sampling as such, if the higher neutrophil counts with capillary sampling are, as Dr Shohat suggests, induced by demargination of granulocytes because of release of adrenaline caused by the pain of the sampling procedure itself.

Ethical considerations precluded capillary sampling both before and after arterial sampling, and a direct comparison of venous and capillary sampling, but it would have been interesting to have had two groups, one in which capillary sampling preceded arterial sampling and one in which it was done afterwards. Our data did not show a variation in the white cell count, and I wonder what mechanism Dr Shohat proposes for his observed rise during and after lumbar puncture.

These points emphasise the difficulties in establishing a reference range of white blood count values for infants, particularly preterm infants, and in interpreting results by comparing them with published ranges. Application of the International Committee for Standardisation in Haematology guidelines for the standardisation of blood specimen collection procedures for reference values is obviously impractical, but it is clear that the method of sampling does affect the results obtained. Many of the published ranges are based almost entirely on capillary sampling so that arterial sampling, which is commonly done in these intensively monitored infants, may lead to a diagnosis of neutropenia. Conversely, as Dr Shohat points out, a painful procedure performed shortly before sampling might cause a neutrophilia equivalent to that found in older children and adults after exercise.

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[1] Christensen RD, Rothstein G. Pitfalls in the interpretation of leucocyte counts of newborn infants. *Am J Clin Pathol* 1978;**72**:608–11.

# The metabolic load of stored blood. Implications for major transfusions in infants

Sir,

In a recent article Ratcliffe *et al*[1] described the changes in plasma osmolality, electrolyte balance, and metabolic substrates that can occur during storage of blood. These changes, an increase in osmolality, potassium, and lactate concentrations, and a decrease in sodium concentration, were ascribed to alterations in red cell permeability and continuing metabolism during storage. Infusion of large amounts of such stored blood may be harmful to the sick infant and may, for instance, result in severe hyperkalaemia.[2]

Interestingly, storage of fresh frozen plasma (FFP) can also produce solute concentration gradients in the infusion bags. We describe (table) the osmolality and solute concentrations incidentally measured at the surface and at the bottom of a bag containing 'unshaken' thawed plasma. To confirm this finding, we stored FFP in five 20 ml glass tubes and subsequently thawed the samples at room temperature without shaking. The following mean (SD) plasma osmolality and sodium concentrations were recorded: 237 (5) mOsm/kg and 33 (5) mmol/l at the surface, and 425 (18) mOsm/kg and 199 mmol/l at the bottom. Thorough mixing of the plasma resulted in homogenous concentrations of 321 (5) mOsm/kg and 173 mmol/l.

The differences in osmolality and concentrations in a cell free solution probably occur during freezing, which starts at the surface, and the free water is frozen first. We conclude that the infusion of large amounts of unshaken thawed plasma could harm a sick neonate, and that this phenomenon could affect the accuracy of chemical analysis of samples of thawed plasma.

Table *Osmolality and electrolyte concentrations from surface and bottom of unit of unmixed thawed plasma*

| *Measurement* | *Surface* | *Bottom* |
|---|---|---|
| Osmolality (mOsm/kg) | 237 | 679 |
| Sodium (mmol/l) | 127 | 277 |
| Potassium (mmol/l) | 2·6 | 5·2 |
| Chloride (mmol/l) | 57 | 92 |
| Glucose (mmol/l) | 21 | 40·7 |
| Creatinine (μmol/l) | 50 | 100 |
| Protein (g/l) | 43 | 114 |

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# Endotracheal resuscitation of preterm infants at birth

Sir,

The meticulous studies into the mechanics of neonatal resuscitation carried out by Professor Milner and his colleagues over the last few years provide a unique and valuable body of information. I would, however, like to clarify certain points relating to the methodology and interpretation of their most recent work.[1] In particular, how might the flow resistance of the resuscitation equipment affect the efficacy of resuscitation? The authors do not state the flow rate into their resuscitation circuit. The fact that their pneumotachograph was linear to 15 l/minute implies that an inspiratory flow rate up to this value could be provided for.

Careful analysis of figure 1 would suggest that the effective inspiratory flow resistance of the resuscitation circuit was very high. In the figure, the 'inspiration response' of the baby caused a peak inspiratory flow rate of 5 l/minute (0·08 l/second). This was achieved only by reducing the pressure at the endotracheal tube to −8 cm $H_2O$. Thus the apparatus resistance (resistance pressure/flow) was at least 100 cm $H_2O$/l/second, compared with the intrinsic resistance of an intubated preterm baby of roughly 200 cm $H_2O$/l/second.[2] Could this be part of the explanation for the very small tidal volumes achieved?

Finally, figure 3 needs further explanation. In it a injection pressure of 25 cm $H_2O$ is achieved with an expiratory flow rate of 1·3 l/minute. Firstly, how can airway pressure rise to such a level at such a low flow rate unless the expiratory resistance of the circuit and blow-off volume are very high? Secondly, how did the baby manage to breathe out with an intrathoracic pressure of about +15 cm $H_2O$ against an inflation pressure of +25 cm $H_2O$? The answer may be that the oesophageal pressure measurements in young infants by this technique are so unreliable[3] that their use even for timing the babies' respiratory efforts are highly questionable.

**References**

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Dr Hoskyns and Professor Milner comment.

We are grateful for Dr Silverman's interest in our paper. The flow resistance of the resuscitation equipment was 16 cm $H_2O$/l/second and 7 cm $H_2O$/l/second with endotracheal tubes of internal diameter 3·0 and 2·5 mm, respectively. These measurements were obtained using the inspiratory flow rates used for the studies—that is, three litres per minute—although we would now recommend that flows of at least six litres per minute are used in order to overcome the inflation pattern shown in figure 1. This has occurred because the baby has breathed in faster than the flow of air to the resuscitation circuit. Under these conditions the circuit resistance can be considered as infinite, as this is effectively a closed system.

We do not find it surprising that the airway opening pressure rises if a baby makes expiratory efforts during a period of inflation. In this situation the resistance is not just that of the resuscitation equipment but will include all the circuit back to the pressure relief valve of the resuscitator.

Finally we would entirely agree that oesophageal pressure measurements in immature babies are likely to be unreliable quantitatively but consider that this does not invalidate their use for timing events in the respiratory cycle.

## Prediction and management of nocturnal hypoglycaemia in diabetes

Sir,

Whincup and Milner have shown that under standardised conditions in hospital nocturnal hypoglycaemia can be predicted by a blood glucose concentration of less than 7 mmol/l at 10 pm, and that nocturnal hypoglycaemia can be largely prevented by a 10 g snack of carbohydrate for those with a blood glucose below 7 mmol/l.[1] Their advice therefore for parents managing children at home, or presumably doctors managing children at British Diabetic Association (BDA) Holiday Camps would be to test the blood glucose before bed and give a 10 g snack if the blood glucose was low. Anyone who has attended BDA Holiday Camps, however (including Whincup and Milner), will agree that life is never so simple. I have collected data from two holiday camps to determine if symptomatic nocturnal hypoglycaemia can be prevented. Under BDA rules no 'extra' blood tests or interventions that might upset camp life can be imposed on the children, so the data were collected from the record cards that the children normally complete at camp.

At one camp 16 children aged 12 to 16 years went to bed at 10 pm, two hours after their last snack. Tests for blood glucose were performed on 81 occasions and on 39 the result was ≤7 mmol/l. The children were given carbohydrate according to the following sliding scale: glucose concentration 2 mmol/l, 30 g carbohydrate; 4 mmol/l, 20 g; 7 mmol/l, 10 g. On 87 occasions no tests were performed. Overall the results were: blood glucose concentration at 10 pm ≤7 mmol/l, one episode of nocturnal hypoglycaemia; >7 mmol/l, six episodes, and where the test was not done, one episode.

At the second camp there were 43 children aged 8 to 10 years. These children went to bed straight after a snack. Their blood tests were performed at 8 pm (before the snack) and carbohydrate given according to the same sliding scale. Tests were performed on 215 occasions and were ≤7 mmol/l on 120 occasions. Blood tests were not performed on 377 occasions. Overall the results were: blood glucose concentration at 8 pm ≤7 mmol/l, 12 episodes of nocturnal hypoglycaemia; >7 mmol/l, two episodes; and where the test was not done, 10 episodes.

There were just as many hypoglycaemic episodes when those who had a glucose concentration ≤7 mmol/l were given carbohydrate as there were when tests were not done and nobody was given extra carbohydrate. The value of tests before bed at camp must therefore be questioned. Camp and home conditions, unlike hospital conditions, allow all sorts of compounding factors to creep in and tests at camp may not be that accurate. Moreover we did not test the younger children at 10 pm because that would have been too intrusive.

I suspect that Whincup and Milner's data would not look so convincing if they had carried out their trial under more 'free range' conditions.

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*hives of Disease in Childhood,* 1987, **62,** 1201–1203

# ook reviews

**anasia and the Newborn. Conflicts
arding Saving Lives** (Series· Philosophy
Medicine 24). Edited by R C McMil-
H T Engelhardt Jr , S F Spicker. Pp
US $39·50, £42·75 hardback D Reidel
Co, 1987

ally I intended just to 'dip' into the
k but the comprehensive lengthy intro-
ion aroused my curiosity to learn more
ut what the lawyers, ethicists, geneti-
, historians, philosophers, theologians,
practicing physicians had to say about
most emotive subject in paediatrics.
he book starts with a good review of
religious origins of the sanctity of life.
akes us from pagan times through
o-Christian heritage to the post-
istian era This is accompanied by an
llent review on religomoral dilemmas
g the caring professions in their
roach to defective neonates.
hough not relevant to this country, the
ys on American state and federal reg-
ions bring home how lucky we are in
country to be spared the cumbersome
bureaucratic regulations which govern
ntal decision making regarding their
ctive neonates. In this context every-
should read the Baby Doe con-
ersy
the chapters which follow various
ors have argued well the case for active
anasia, taking into consideration the
gious, moral, and social issues raised by
topic. Both the financial and psycholo-
l implications of aggressive manage-
t of deformed babies are discussed in
th, as are the burdens this approach will
ose on the family and the society.
re is a detailed analysis of harms and
efits promised by different levels of
rvention Arguments have been put
ward for both state legislation and ethics
mittees to oversee active euthanasia.
is country I believe most paediatricians
ld favour the view put forward by Duff
Campbell. They argue that only caring
sons can make caring decisions, with
hasis on a family orientated approach
parents actively involved in decision
ing with paediatricians providing the
fessional guidance required.
hough most neonatologists would be
iliar with Sinclair's economic evalua-
of the effectiveness and efficiency of
neonatal care, I would recommend it to all paediatricians undertaking intensive care of the new born

The book has been well edited, each author knowing what has been written by others The chapters are well coordinated and the references and indexing carefully prepared Some chapters are heavy going and need to be read more than once

My main criticism is that for the book to be more relevant in this country, more than one British paediatrician should have been selected. We live in a post-Christian era with a multireligious culturally mixed society It would have been helpful to have had some information about other religious beliefs. For a practicing paediatrician faced with a defective neonate of Moslem or Hindu parentage, this book would give no guidance. Perhaps this could be incorporated in any further symposia organised on this subject

I recommend this book to all concerned with the management of defective neonates including paediatricians, family physicians, midwives, and social workers It will certainly generate a lively debate on this most emotive issue

S K M JIVANI

**A Neonatal Vade-Mecum.** Edited by P J Fleming, B D Spiedel, and P M Dunn Pp 344 £13·50 paperback Lloyd-Luke (Medical Books Ltd), 1986

This book is a practical guide to neonatal care aimed at senior house officers. The first quarter of it deals with 'perinatal' matters, like the high risk pregnancy, delivery room care, birth trauma, care of the normal baby, care of the high risk baby, transport of the sick baby, and congenital abnormality The middle half of the book is system and disease orientated, covering all the expected topics including lung disease, heart disease, renal disease, surgical problems, infection, blood disorders, neurological disorders, metabolic disorders, nutrition, and jaundice. The final quarter consists of chapters on broader aspects of neonatal care, such as care of the family (which includes the addresses of self help groups), nursing care, practical procedures, documentation, and audit, developmental follow-up, drugs and prescribing, ethical issues, and normal laboratory and physiological data.

The amount of information which has been packed into this truly 'pocket sized' book is remarkable, though this does mean that the rate of unloading of information is very high, making the text hard work for anyone completely new to the subject It is, however, perhaps more a book to 'look things up in' than to read through systematically. The text has ample sub headings, which is a definite aid to comprehension, and the indexing and the quality of diagrams is satisfactory.

As would be expected from the source of this book, there is little of importance to disagree with in either the factual content or the authors' views on management, I would be perfectly happy for my senior house officers to put the recommended practices into action There are one or two local oddities which would not go down well everywhere, but none of us, alas, is immune from those. I recommend this book wholeheartedly

P R F DEAR

**Children's Hearing Problems: Their Significance, Detection and Management.** By Joyce Tweedie Pp 105· £8·95 paperback. Wright, 1987

Regrettably hearing problems in children are frequently missed or misunderstood by many doctors, few of whom have had any specialist audiological training This book was written in an attempt to redress the balance and is particularly directed at those to whom parents often turn for advice This includes general practitioners, clinical medical officers, and doctors in related fields such as ear, nose, and throat surgery and paediatrics. It would also be useful to other groups of workers, such as speech therapists, health visitors, and teachers. Just under half of the book is devoted to the basic sciences essential to an understanding of audiology. There are simple, clear chapters on anatomy and physiology of hearing, acoustics, and tests of auditory function in children, as well as a section on amplification and the types of hearing aids in current use

Current methods of screening for hearing loss in the community are discussed, although 'performance tests' and speech discrimination tasks, which are widely used as screening techniques in children aged 3–5 years, are confusingly included in diagnostic audiometry The author suggests that the audiological management provided in her district could be regarded as a model for future developments and describes it in some detail A similar service could, however, be provided by districts with different staff and facilities

The sections covering the effects of hearing loss on the child concentrate on the more prevalent condition of secretory otitis media, with the author's bias in favour of active management being strongly stated There is less emphasis on sensorineural hearing losses. This balance may be reasonable in view of the potential market for this book Overall this is a clear, concise, and informative book on these aspects of paediatric audiology of interest to the non-specialist and as such deserves a wide readership.

S BELLMAN

**Child Psychiatry. A Developmental Approach.** By Philip Graham Pp 465. £12·50 paperback Oxford University Press, 1986

This book aims to provide a contemporary summary of child psychiatry for all doctors concerned with children, but especially paediatricians and psychiatrists in training.

ICD 9 and DSM III, which are not food additives but rival multiaxial systems for classification of psychiatric disorders, are assessed and their limitations noted. Clear accounts of the various disorders are presented within a developmental framework. Competing aetiological theories are mentioned but emphasis is placed on the known facts of epidemiology, characteristics and prognosis of each condition Psychosocial aspects of physical diseases are well covered. Some paediatricians may find the summaries of medical aspects of the various illnesses and handicaps to be superfluous, but their inclusion provides useful background information for readers from other disciplines.

Treatment methods are reviewed impartially Many examples of different approaches are given, illustrating appropriate interventions by general practitioners and paediatricians, as well as by more specialised therapists The book concludes with a section on preventive approaches Primary prevention will depend mainly on public policy There is, however, plenty of guidance to individual professionals to improve their personal practice by enhancing communication, fostering children's self-esteem and promoting healthy attitudes within families

If there has been any tendency for paediatricians to imagine child psychiatry as a marginal discipline practiced behind one way screens, this book provides a welcome overview which places a concern for psychosocial issues firmly at the heart of paediatrics. It is concise, well referenced, and remarkably inexpensive.

D B CUNDALL

**Oxford Monographs on Medical Genetics No 15. Duchenne Muscular Dystrophy.** By Alan E H Emery Pp 315. £35·00 hardback. Oxford University Press, 1987.

A whole book devoted to a single disease must suggest to many that the finished product will be a detailed text written for a small number of highly specialised clinicians or research workers Professor Emery's book is detailed and could without doubt be of interest to such a group of readers, but to many others besides. Sir John Walton in his Foreword cites a wide range of professionals, not all of them medical, that he thinks would find something of interest within this book I agree with him

Professor Emery's monograph on Duchenne muscular dystrophy begins with an introduction to some general principles on the development and morphology of muscle followed by an interesting account of the historical aspects of the disease. Subsequent chapters cover the clinical features, the diagnosis, differential diagnosis, discussion of the involvement of tissues other than skeletal muscle, the biochemistry of Duchenne muscular dystrophy, pathogenesis, genetics, molecular pathology. prevention, genetic counselling, and management. There are seven appendices and each chapter has a short summary A comprehensive and apparently well chosen bibliography is provided and this includes a large number of references to publications within the last two years

The style of the book is attractive and it is enjoyable to read although typographical errors are quite common

The account of the molecular patho of Duchenne muscular dystrophy is example of how a complex and rap changing subject is presented in a form should be comprehensible to most read And it is very up to date. The large cha on management succeeds in strikin realistic balance, for the most part, tween the varying thoughts of diffe schools on what cannot avoid being emotive topic I believe that this is a b that should be available in every paedia library and that all of those that have role in the diagnosis and managemen children with neuromuscular dis should be made aware of its existence encouraged to look at it.

The number of people who may wan buy the book may be small, but those would welcome access to it will, I am s by numerous

GWILYM HOSK

**Children with Neurological Disord Book 1. Neurologically Handicapped C dren: Treatment and Management.** Ed by N Gordon and I McKinlay. Pp £19·50 paperback, £42·50 cloth Black Scientific Publications, 1986.

**Children with Neurological Disord Book 2. Neurologically Sick Child Treatment and Management.** Edited b Gordon and I McKinlay Pp 525. £1 paperback, £42 50 cloth. Blackwell Sc tific Publications, 1986

These two companion volumes expl similar fields: the neurology managem of handicapped children (book 1) and s children (book 2) Such artificial dist tions cause considerable overlaps Boo covers long term handicaps, (such as ebral palsy, hearing loss, fits and learn disorders) and management approac (orthopaedics, genetic counselling, medial teaching), with some philosoph discussion. Book 2 reviews paedia neurological disease, (including infecti tumours, traumatic and metabolic eases), and management issues (neuro gical referral, respiratory failure, couns ing, neuroradiology)

The 40 contributors, half of whom w in Manchester, range from neurolo and neurosurgeons (predominant in b 2) to psychologists, social workers, ger cists, and other therapists The intentio to update neurological management, book 1 is aimed not only at doctors he general effect of reading these imes straight through is of attending a multidisciplinary symposium There epetition, extreme variation in style, tent, and complexity Some contribu- use that lame phrase, 'space does not nit . ', others describe, with detailed es, obscure neurological rarities Other iors forget that 'treatment and manage- t' is their remit There is a shortage of onal attention, though they appear (in square brackets) as referees dur- a virulent dismissal of signing for deaf dren—maybe to placate its advocates where Book 1, too often, is discursive, a stately vagueness, ('not infrequent', tively common') and insufficient con- porary data and controlled results of vention David Taylor's characteristic ributions are delightful—his case his- s are compelling—but he needed re- ding not to tell the same story twice extbooks are best not produced in two mes, and without a common index se 930 pages could be reduced to 500, g the ruthlessness of journal editors, e chapters can be jettisoned The erback volumes, however, are remark- cheap, and include contributions that well researched, packed with contem- ary references, and of immediate help e management of ill and handicapped dren

J W PARTRIDGE

**Adolescent Years: The Ups and Downs rowing Up.** By J Buckler Pp 152. 0 hardback Castlemead Publications, e, 1987

he first half of this book Dr Buckler ribes the events of puberty while the nd part contains information about the ciated features of adolescence. As one ld expect from this author, the former omprehensively dealt with while the r contains an account of many of the lems that may concern a teenager The s expressed are those of a caring nt as well as those of a specialist in vth and development I was particu- impressed at the sensitive way in which the more delicate subject matter was discussed It is unfortunate that adolescent medicine is poorly represented in the United Kingdom and many associated problems fall in between the specialities of paediatrics and adult medicine Fortunately, Dr Buckler's book provides much material to unify these subjects

I was delighted that large sections of the text were devoted to psychological development My main criticism, however, is that important issues such as drug dependency, contraception, and unwanted pregnancy were allocated an inappropriately short discussion and, of greater importance, practical guidance was limited

There have been several books about adolescence published recently but I believe this to be one of the better ones. The cost is reasonable, especially considering this is a hardback edition Although written primarily for parents and associated health workers, I am sure this book will be most eagerly received by teenagers themselves, to whom I shall have no hesitation in recommending it

R STANHOPE

**Fluid Therapy in Childhood.** By T L Chambers Pp 140: £8·50 softback. Blackwell Scientific Publications, 1987

This short book is designed to be read while waiting for laboratory results or watching an ill patient; it will be a great help to all those who have that responsibility It provides uncomplicated advice on choosing the correct biochemical tests, the accurate interpretation of the results, and the safe, immediate treatment of a sick child The first third of the book considers the theoretical principles governing fluid balance, the normal mechanisms of regulation, and the aetiology of pathological states The terminology is simply defined The tables and figures are outstandingly clear The calculations of normal needs and abnormal replacements are provided, and the enteral route is not considered outdated The rest of the book discusses the commoner circumstances in which the body's regulatory mechanisms become disordered gastroenteritis, diabetes mellitus, kidney disease, adrenocortical failure, hypercalcaemia, poisoning, and surgery There is a particularly helpful chapter by Mr R W Griffiths on the burned child, which recognises that most of these problems are not dealt with by paediatricians The sections on calcium and parenteral feeding are short and rather disappointing, but overall several quarts of guidance have become an excellent pinta. It will be worth keeping a copy on each paediatric ward

A N STANTON

**Drawings from the newborn. Poems and drawings of infants in crisis.** By H Spears Pp 127· $39·95 hardback Ben-Simon Publications, 1986

This is an unusual book containing 20 poems and 52 full page pencil drawings of babies done by an American artist in a neonatal intensive care unit in Copenhagen The drawings show babies in incubators with tubes and all resuscitation equipment, the size of the children is often shown by contrast with the hands of the nurses. The drawings are competent and of variable quality with tone values much like those of the well known books of drawings by Dowd, but she has barely Dowd's facile skill The poems are accompaniments or substitutes for drawings The whole gives a fascinating insight into an artist's view of a situation usually only recorded by a nurse or doctor or by an involved relative Some of the poems have beautiful passages such as 'Any kind/of life is life,/but here the event conceals all questioning/ . . .' and '. on the screen, this tiny green snake/of her life whips and whips and whips'

This is not a happy book any more than any other book on human tragedy is, but it is a true work of art in that it will leave every reader a little more thoughtful and a little different. It is an excellent book to give to someone who has lived through an intensive care ward; I can see many neonatologists being given a copy from a 'grateful patient'.

JOHN L EMERY

*Archives of Disease in Childhood,* 1987, **62,** 1204

## *British paediatrics*

# Primary health care

In its response to a Department of Health and Social Security (DHSS) document *Primary health care: an agenda for discussion*, the British Paediatric Association (BPA) emphasises the fact that departments of paediatrics in university hospitals in inner city areas are providing a considerable amount of primary care for local children. If alternative arrangements cannot be made this service should be appropriately funded. The point is also made that reductions in university finance are seriously limiting the contribution that academic departments of child health and general practice can make to the training of general practitioners.

The Association welcomes the recommendation that general practitioners should work in community child health but would like to be assured that there will be adequate postgraduate training for this work and that general practitioners will be able to devote more of their time to the care of children. The timing and content of screening procedures is currently being examined by a joint working party of the BPA, the General Medical Services Committee of the British Medical Association, and the Royal College of General Practitioners. The BPA hopes that no firm policy will be laid down until this working party has reported. The DHSS document makes no mention of the school medical service. This may have been deliberate if the government sees this service as secondary care. The BPA has sent its own working party report on school health services to the DHSS and would welcome the opportunity to discuss the matter further.

# Neighbourhood nursing

The BPA has responded to another DHSS report *Neighbourhood nursing—a focus for care* in somewhat critical terms, indicating that it does not accept the premise that current arrangements for community nursing need the proposed radical revision.

The DHSS report seems to have almost totally ignored the needs of children and has disappointingly overlooked the BPA's recommendations for a community nursing component in the district child health service. The care of sick children in the community demands the specialised training required for the Registered Sick Children's Nurse Certificate rather than general district nursing experience. The BPA rejects the notion that specialist children's nurses working in the community—for example, in oncology or dialysis—should be under the management arrangements of the neighbourhood nursing service. These nurses are part of the secondary care team, sometimes replacing and at other times supporting the primary care nurses.

Although the recommended checklists are accepted by the BPA as an aide memoire they are not comprehensive and should not be used inflexibly. Some of the checklist items are naive or obscure and those dealing with the community child health services are of limited value. For example, the role of the District Handicap Team is ignored and the items on child abuse do not refer to the current DHSS recommendations.

In the Association's view the report places too much emphasis on management and not enough on working nurses, especially in its manpower recommendations. Indeed, the proposed increase in responsibilities and status of nurses could make the managerial arrangements superfluous.

A D M JACKSON

# Monatsschrift Kinderheilkunde

Organ der
Deutschen Gesellschaft
für Kinderheilkunde

135. Band
Heft 8
August 1987

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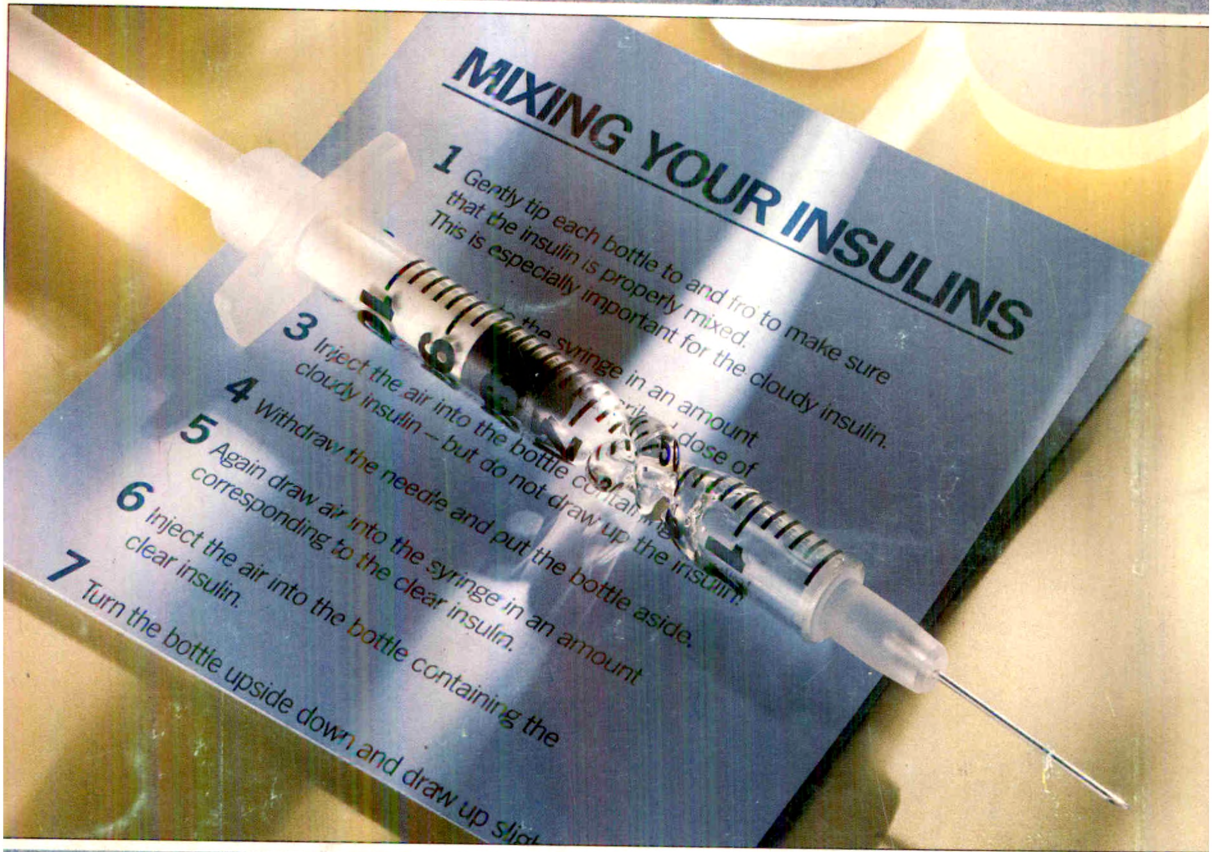

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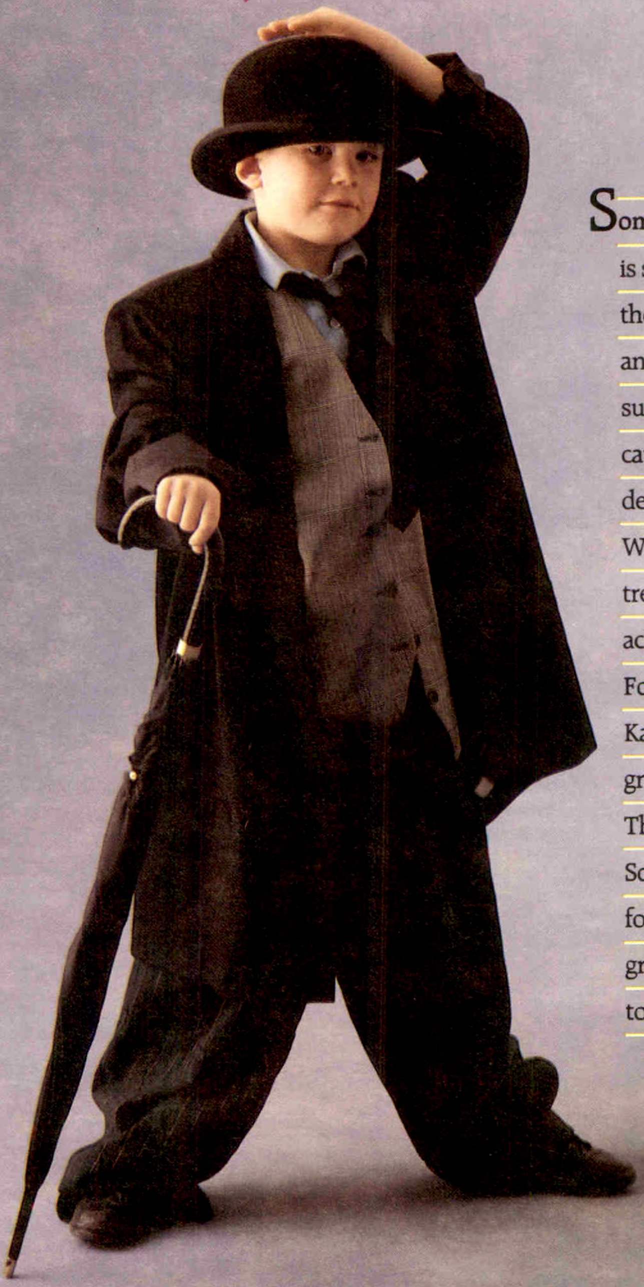

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# Monatsschrift Kinderheilkunde

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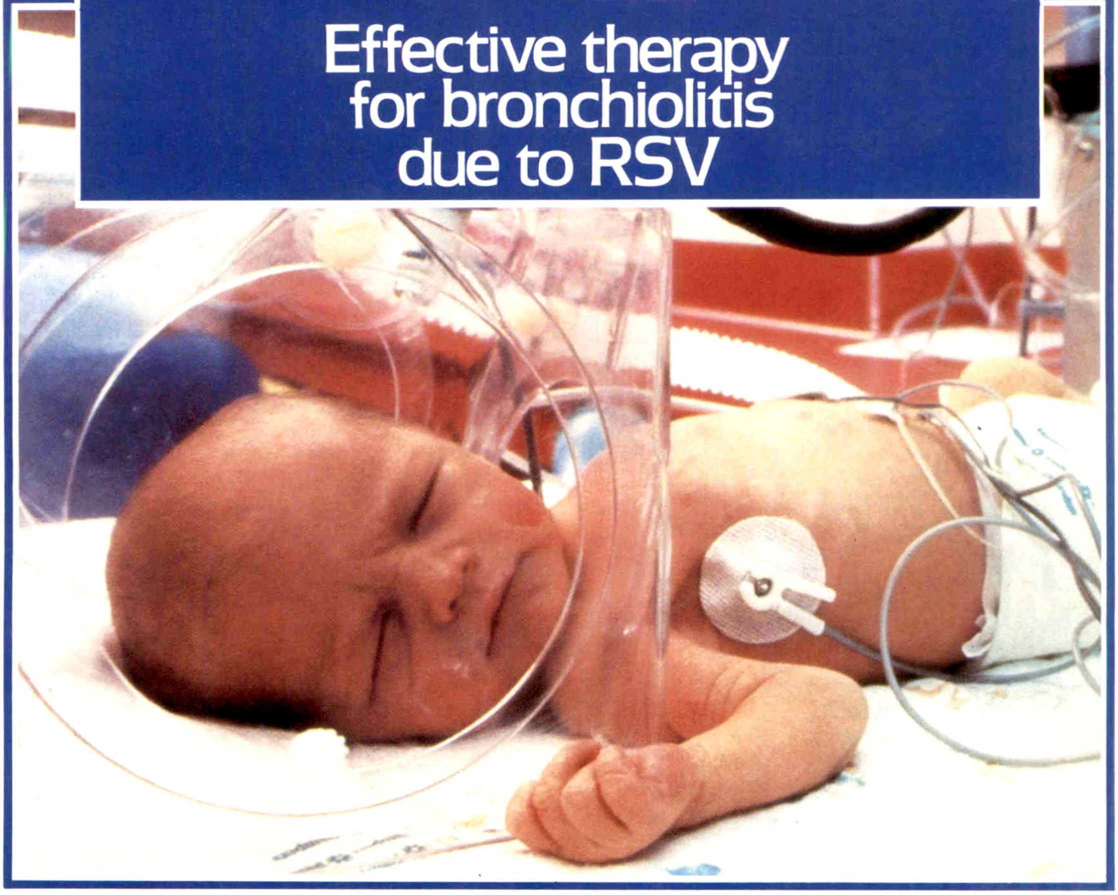

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*Archives of Disease in Childhood,* 1987, **62,** 1205–1206

## *Annotations*

# Placental transport: diversity and complexity

Every mammalian fetus is autonomous, being separated from its mother by a layer of fetal membranes. To allow nutrition, respiration, and excretion fetal blood flows through an extracorporeal circulation close to the mother's blood in the placenta. There are enormous and unexplained differences in placental architecture among species, more than are found in any other mammalian organ. In pigs the placenta is a simple corrugated membrane; in sheep it consists of some 50 individual miniplacentas. In both these species fetal and maternal blood remain mainly in capillary circulations separated by a multilayered epithelium formed of both maternal and extraembryonic fetal tissue. In human fetuses, by contrast, fetal blood flows through villi in which the capillaries are covered only by fetal tissue which bathes directly in the intervillous space in a pool of flowing maternal blood. Rat, mouse, and guinea pig placentas are similar, but these species have a subsidiary yolk sac placenta which transports immunoglobulin and which is absent in humans.

The outermost layer of the fetal membranes is trophoblast, which insulates the amnion, placental circulation, and fetus from the mother. Human trophoblast comprises several subpopulations of cells and also a syncytium.[1] It is metabolically active and contains enzymes which may be induced by maternal smoking and which can modify foreign compounds. It invades maternal tissue, but only to a controlled extent. Its limited expression of fetal histocompatibility antigens plays a part in the complex mechanisms that prevent rejection of the fetus by the mother. The trophoblast produces a wider range of hormones than any other tissue, and the large number of different receptors it bears on its surface for such molecules as insulin, epidermal growth factor, opioids, and catecholamines suggest that it may also function as an endocrine end organ. In addition, the placenta is an organ that carries out the transport tasks performed in postnatal life by alveolar epithelium, renal tubules, gut mucosa, and hepatocytes.

### Transport mechanisms

There are several modes of transport across the placenta.[2 3] Relatively lipid soluble molecules such as respiratory gases, anaesthetic agents, many other drugs, and unconjugated bilirubin cross easily by penetrating the cell membranes of the placenta. Small water soluble molecules such as urea and water itself also cross easily down diffusional or osmotic gradients and may do so through minute pores of molecular dimensions[4 5]; these, however, have not been convincingly shown by electron microscopy and are a little difficult to reconcile with the syncytial nature of human trophoblast because in other tissues pores are usually between cells. Small electrolytes may also cross by this route. Transfer of glucose is markedly facilitated by a specific carrier molecule, but it is not actively transported. Most amino acids, calcium, and perhaps potassium and phosphate, are transported from mother to fetus by specific carrier mediated processes, but these—unlike that for glucose—consume energy and carry out active transport, leading to higher concentrations in fetal than maternal plasma. Immunoglobulin G (but not A, M, or E), iron, and vitamin $B_{12}$, are taken into the trophoblast by receptor mediated endocytosis and then released by a poorly understood mechanism into the fetal circulation.

Diversity among species means that simple extrapolations from experimental animals to women are not permissible but many mechanisms are the same in different species—for example, the carrier systems for calcium, amino acids, and glucose. Other transport systems, such as those for iron or for immunoglobulin, may be radically different as is the passive permeability to less soluble drugs. Animal studies are better used for building up a clear picture of how placental transport works as a whole rather than for answering specific clinical questions, though the latter is often unwisely attempted.

### Control of placental transfer

Little is known about the control of placenta permeability. The rate of transfer of highly permeative lipid soluble molecules such as those mentioned above is not affected by thickening or thinning of the placental tissue barrier but rather by the rate of blood flow in maternal and fetal circulations and by their geometrical relationship to each other. Their transfer is said to be 'flow limited'. Large increases in placental blood flow as gestation proceeds are important so that the transport of respiratory gases can be increased to meet the needs of the growing fetus. Short term modulation of blood flow does not seem to be an important physiological control mechanism, but reductions may reduce gas transfer in disease.

The permeability of lipid insoluble substances which cross more slowly is hardly affected by changes in the rate of blood flow. Their passage is, by contrast, 'membrane limited' and any control of their transfer is likely to be by a change in placental tissue carrier mechanisms. An example of membrane limited control in the placenta is the ability of the rat placenta to keep a fetus normokalaemic when the mother is hypokalaemic,[6] and there are hints of similar mechanisms for calcium and for amino acids. The ability of the pig placenta to increase sodium transport towards the fetus under the influence of fetal catecholamine in vitro may represent another control process.[7] It is not known if controls such as these are important in humans.

## Transport and disease

It seems certain that abnormalities of placental transport contribute to fetal disorder, but there is little direct evidence to support this—apart from the general association between the placenta's poor growth, abnormal histology and disturbed endocrine function, and some cases of intrauterine growth retardation and maternal gestational disease. Maybe we have not always looked at the right conditions Spontaneous abortion or fetal death, congenital malformation, transient perinatal diseases such as nonimmune fetal hydrops or neonatal hypocalcaemia, or problems not apparent until later childhood (such as cerebral palsy) might all reasonably on occasion be attributable to placental transport defects, but we have no direct evidence for this. Normal transport of unwanted maternal plasma constituents—IgG leading to neonatal disease or fetal heart block in maternal immune disease, or fetal infection by those viruses which affect the fetus before term—might also be preventable if we could develop means of manipulating placental transport mechanisms.

To progress the techniques now becoming available must be applied: amniocentesis (though amniotic fluid constituents, notably proteins, may reflect maternal rather than fetal plasma),[8] placental villous biopsy, non-invasive placental imaging and blood flow studies, heavy isotope techniques, and the ability to sample fetal blood in utero before labour.[9] Each of these approaches, however, provides only one piece of a complicated jigsaw puzzle. For satisfactory evaluation of the data they provide, their use must be linked to a clear understanding of placental physiology and to an alertness that a placental defect might be the cause of a specific clinical problem in the fetus, newborn, or older child.

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# Investigation of perinatal death

The progressive fall in fetal and perinatal mortality in the developed world has accentuated the tragedy of this unexpected event to the family and has increased pressure on clinicians and pathologists to provide an explanation and an accurate prognosis for future pregnancies. Adequate investigation of a perinatal death often entails cooperation between obstetrician, neonatologist, pathologist, and clinical geneticist and may require a range of specific laboratory tests.[1]

Several studies have evaluated perinatal necropsies in recent years and have confirmed the value of the procedure.[2-5] A recent study in Colorado claimed that necropsy was the only means of establishing the cause of death in 26% of cases and that necropsies were the sole source of information, indicating the need for genetic counselling in 48% of deaths where this service was required. A study performed in 1980, however, showed that in Britain only 61% of stillbirths and 54% of neonatal deaths had necropsies and in only 18% of deaths was the examination performed or supervised by a perinatal pathologist.[6]

## Motivation

The interdepartmental approach required for investigation of a perinatal death is prone to failure due to economic or operational stresses or sheer lack of interest by one or other of the departments involved. A recent survey carried out by a subcommittee of the Royal College of Obstetricians and Gynaecologists found a wide range in the frequency with which necropsies were requested and in the adequacy of the studies carried out at different centres throughout Britain.[7] Where pathologists are unable to or not sufficiently interested in providing an adequate service obstetricians and paediatricians lose interest with the result that requests for necropsies decrease. The pressure for a full investigation of each perinatal death and the establishment of an adequate service in perinatal pathology must come from the clinicians who have the task of explaining the death to the parents and of formulating an appropriate strategy for the management of future pregnancies. The tools which are now available to the clinician, including cytogenetic, enzymological, and molecular methods of diagnosis and imaging techniques for the study of structure and function ensure that obstetricians, paediatricians, and clinical geneticists are deeply concerned with establishing the nature of any disease detected in the living fetus and newborn infant. Investigation of the fetus or newborn infant who dies, with or without such studies, is merely an extension of such a process.

## Role of the clinician

At a practical level the clinician, an obstetrician in the event of fetal death and paediatrician in cases of neonatal death, has the task of starting and coordinating investigations. Many obstetric and neonatal units now have a check list of procedures to be carried out. These include taking samples for haematological, microbiological, and cytogenetic tests, requesting permission for necropsy, completing the necessary request form for necropsy to provide a summary of the clinical details for the pathologist, and taking a photograph of the baby for the parents Maternal studies which have been recommended as a routine if not performed antenatally include plasma antibody screening tests for toxoplasma, rubella, cytomegalovirus, and herpes simplex, Kleihauer test, Venereal Disease Research Laboratory test, tests for rhesus or other antibodies, tests for thyroid function, and measurement of glycosylated haemoglobin and glucose tolerance test.[7]

In cases of neonatal death the need for any tests before the necropsy has been carried out depends on the extent to which it has been possible to study the infant in life and the facilities which are available to the pathologist. When dealing with an undiagnosed hydropic neonate it is important to take cord blood for haematological and microbiological studies, to save plasma and ascitic fluid for possible further studies, and even to set up a fibroblast culture for cytogenetic or metabolic studies.[1 8] If an infant dies after prolonged intensive care, all necessary clinical investigations may have been completed leaving only one or two queries to be addressed by necropsy. If there are no facilities for radiology in the pathology department the clinician needs to have *x*-ray pictures taken before necropsy in cases of malformations of the skeleton such as short limbed dwarfism, and in cases of non-immunological hydrops. If there is a clinical geneticist is available, he or she can provide a valuable coordinating link in these activities.

**Role of the pathologist**

The primary role of the pathologist is to supplement the observations of the clinician by carrying out external examination, measurement, dissection, and histological examination, as well as any additional studies that are indicated during the procedure.[9–12] It is therefore essential that the pathologist, particularly if he is a trainee or non-specialist pathologist, should be given full clinical information and encouragement by the clinicians. The high proportion of useful necropsies reported by the Denver group may be in part attributable to discussions beforehand between the trainee pathologist and the clinical geneticist in all cases.[5] A close clinicopathological link of some kind is particularly important at a time when the adult necropsy rate is declining and there is a shift in emphasis in pathological training away from the gross observational skills needed in the postmortem room. The ability to recognise minor macroscopic deviations from normal is necessary if appropriate further laboratory investigations are to be selected in cases of infection, obscure malformation, or metabolic disease; photography and the eyes of other clinicians are invaluable aids. A paediatric or perinatal pathologist may have less need of such help from his or her clinical colleagues but is equally dependent on having a full clinical history. The pathologist needs to provide interim and final reports promptly to the clinicians and to keep them informed of the progress of any special investigations so that the findings can be explained to the parents.

**Investigations in the absence of consent for necropsy**

Lack of consent for necropsy does not totally preclude performance of diagnostic tests in cases where the cause of death is not known. Here again the prime mover must be the clinician as the pathologist will not normally have information about such cases. There is seldom objection to examination of cord blood specimens or performance of maternal studies as mentioned above. It would also usually be permissable to weigh the infant and make careful external measurements, take whole body photographs and $x$-ray pictures, or investigate internal organs by ultrasound scans (for example to confirm renal agenesis), to culture swabs of external orifices, and to examine the placenta both macroscopically and histologically. Sadly the diagnostic opportunities afforded by this range of studies are often missed by lack of clinical forethought.

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## *Original articles*

# Measles immunisation: feasibility of a 90% target uptake

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SUMMARY A three part investigation of the factors that might influence uptake of immunisation was carried out in Maidstone Health Authority; this included studies of the computer system and attitudes of parents and professionals. Several problems with immunisation scheduling, information transfer between general practitioners and clinics and the computer centre, and validity of computer information were identified. The attitudes of parents, relatives, and friends were generally favourable, although parents reported a lack of knowledge about the disease and vaccine and lack of advice from professionals. Perceived contraindications to immunisation, particularly a history of measles, were important reasons for non-uptake. Professionals' perceptions of contraindications, however, were at variance with Department of Health and Social Security guidelines and none of the recorded contraindications was valid. Calculations of potential uptake suggest that a 90% target uptake is feasible and recommendations are made for changes in services.

A safe and effective immunisation providing lasting immunity against measles has existed since 1968 and yet measles remains a common serious illness. Between 1970 and 1983 there were 270 deaths in Britain from measles and 175 deaths from subacute sclerosing panencephalitis, a long term complication of measles.[1] Notifications of the disease during this period, despite considerable undernotification, ranged from 52 000 to 300 000 a year, with an annual average of 100 000.[2] In Maidstone health district alone about 600 cases are notified each year. Measles also causes some avoidable morbidity; complications from measles were studied in 1976 and showed little change from a study carried out 13 years earlier.[3]

There is national concern that the high incidence of measles should be reduced by ensuring that all eligible children receive immunisation.[2 4] It is difficult to explain the low uptake as measles immunisation has not attracted the adverse publicity that pertussis immunisation has; it requires only one dose; and many health authorities have child health computing systems for administering and scheduling appointments. Several recent studies have suggested that some of the reasons may include poor administration of immunisation services, a lack of commitment among health authority staff, and a lack of understanding of the indications and contraindications of this vaccine.[5–12]

The South East Thames Regional Health Authority (SETRHA) health promotion group recommended that health districts should attempt to achieve a 90% uptake of measles immunisation in the 15 month age group. To help authorities achieve this it is necessary to understand the factors that might influence uptake. This may identify the ways in which people may either be encouraged to use services offered or to change the type of service to improve the location and provision for services for current non-attenders.

When this study was first proposed in 1982 the recorded uptake for measles immunisation in Maidstone was 71%. These figures happened to be the best figures in Kent but were still short of the target. Maidstone District Health Authority uses the standard child health computer system for scheduling immunisation. A three stage investigation of possible factors contributing to the low uptake of measles immunisation was carried out. The stages are (a) a study of the SETRHA version of the standard child health computer system (its functioning and the transmission of information between the various service providers and the computer centre) to establish whether the low uptake of measles immunisation could be partly due to a malfunction in the total information network; (b) a study of the attitudes and beliefs of parents about measles immunisation and parental socioeconomic factors that are associated with the uptake of the service in Maidstone; and (c) a study of the knowledge, attitudes, and beliefs of health professionals about measles immunisation and their potential influence on the uptake of the service

## Subjects and methods

### STUDY OF INFORMATION SYSTEM

In December 1984 the SETRHA computer produced a list from the registered birth cohort of 1981 of all children currently resident in the Maidstone Health Authority. This list, comprising 2356 children, was divided into two groups: those recorded by the computer as having taken up the vaccine (n=1736) and those recorded as not having taken up the vaccine (n=620). Separate random samples were taken with a larger sampling fraction for unimmunised children (as the reasons for non-immunisation were of most interest to us); the immunised children served as a control group. This resulted in 182 immunised and 350 unimmunised children, respectively. Having identified this group of 532 children, the computer system, child health clinic, and general practitioner records were searched for potential reasons for non-uptake. Collection of data took place between December 1984 and June 1985 when all children were at least 3 years old, and consisted of searching these three separate sources for identical items of information that were related to reasons that could explain non-uptake of measles immunisation (table 1). In addition, a search for discrepancies between the three record sources was carried out to identify possible problems in information transfer. For each of the reasons identified (based on the frequency of the reason) the level that the uptake rate could potentially be raised, if the reason was adequately tackled, was calculated.

### STUDY OF PARENTAL ATTITUDES

The SETRHA computer centre produced a list of infants resident in the Maidstone district who would be 13 months old between September and December 1984. A random study sample was drawn from a list of 539 such infants; the remainder formed a control group. A research assistant interviewed the parents in the study group during the week when the child was 13 months old. Of the 199 patients selected for interview, 174 were actually interviewed (a response rate of 87%). The rest had either moved, were not available for interview at three attempts, or in a few cases refused to be interviewed. To avoid

Table 1 *Potential reasons for non-uptake of immunisation*

| *Reason* | *Numbers of unimmunised children (no (%)) (n=347)* | *Potential for change in observed rate of 73 7%* | *Numbers of immunised children (no (%)) (n=182)* |
|---|---|---|---|
| **Related to information system** | | | |
| Change of address during child's first three years (according to clinic or general practitioner) | 48 (14) | +4·0 | 23 (13) |
| No general consent form for immunisation returned to computer centre | 30 (9) | +2 3 | 3 (2)* |
| Received immunisation (according to general practitioner or clinic) but not notified to computer | 5 (15) | +4 3 | — |
| Did not complete course of triple vaccines (according to computer or clinic)† | 84 (24) | +6 4 | 15 (8)** |
| **Not directly related to information system** | | | |
| Consent for measles immunisation withdrawn (according to computer) | 130 (37) | +9·9 | 10 (5)** |
| Consent for all immunisation withdrawn (according to computer) | 19 (5) | +1·4 | 5 (3) |
| Contraindications recorded (clinic or general practitioner)‡ | 99 (29) | +7·4 | 10 (5)** |
| Already had measles disease (according to computer, clinic or general practitioner) | 122 (35) | +9 2 | 9 (5)** |
| Any of these (the above are not mutually exclusive) | 305 (88) | +23 1 | 57 (31) |
| Other reasons | 33 (10) | — | 3 (2) |

*$p<0·005$, **$p<0·001$

†Diphtheria/Tetanus/Polio, this would have prevented scheduling for appointments for measles immunisation.

‡Clinic records listed 106 contraindications for 98 children.

influencing measles immunisation uptake in the study group, questions relating to measles formed just a part of the interview, which was designed and introduced as a survey of parental views of community health services. The possible influence of the interview on uptake was checked by monitoring immunisation in the control group Measles immunisation was scheduled in the normal way when the infants were 14 months old Immunisation uptake was monitored through the child health computer system until the infants were 20 months old. Of the 174 parents interviewed, the children of 43 were recorded as not having taken up immunisation. Attempts were made to follow up these 43 and 40 were interviewed or their whereabouts ascertained. Actual and potential immunisation uptake rates were calculated based on uptake as recorded by the computer records and follow up interviews. Finally, actual uptake rates among socioeconomic subgroupings were compared using $\chi^2$ tests

### STUDY OF PROFESSIONALS' ATTITUDES

A questionnaire was sent to all general practitioners, clinical medical officers, health visitors, and paediatricians in two health authorities: one that had carried out a previous campaign about measles immunisation among health professionals (Maidstone) and one that had not (Canterbury and Thanet). The questionnaire was based on those used previously in similar studies on whooping cough and measles and was modified slightly to suit our requirements.[13] After the question, 'Would you recommend measles immunisation at 15 months in the following circumstances' were 23 statements of typical problems encountered in everyday medical practice concerning measles vaccination. The professionals had the option of responding 'yes', 'yes qualified' (that is with precautions), 'no' or 'not known'. Only in one case was measles immunisation clearly contraindicated, and professionals were expected to make a positive recommendation in most cases. In addition, there were some direct questions on measles immunisation and the disease.

## Results

The main findings of the three studies are presented here, detailed results of each study have been reported separately.[14-16]

### INFORMATION SYSTEM

Table 1 summarises the main reasons for non-uptake identified for 347 unimmunised children in the information system study (basic information was missing for three of these children). Results based on the 182 immunised children are also shown. Measles was recorded by at least one source of information in 122 (35%) unimmunised children· in 28 it was recorded as having occurred before 15 months when immunisation should have taken place. None of the 64 cases of measles known to the computer system was notified until the child was at least 14 months old. Of the contraindications listed, clinic records listed 106 for 98 children, this included those with previous measles disease (50 cases); allergies that were often to eggs (18 cases); a family history of convulsions (18 cases); and a history of convulsions in the child (nine cases). None of the recorded contraindications was found to be valid when assessed against DHSS guidelines.

### PARENTAL ATTITUDES

The results presented here refer to the 174 parents who were interviewed and about whom information was available. The parents' overall attitude to measles immunisation and the attitudes of their relatives and friends were regarded as favourable or neutral in over 90% of interviews; 113 (65%) of parents, however, said that they lacked knowledge about the vaccine and 43 (25%) expressed uncertainties about possible side effects. A small percentage (about 10%) mentioned supposed contraindications in terms of the family or child's medical history (especially fits and egg allergies). By the time their children had reached 13 months, mothers had received little advice about measles immunisation from professionals: 160 (92%) reported receiving no advice from the child health clinic, 153 (88%) no advice from their general practitioner, and 144 (83%) no advice from the health visitor. Professional advice was reported as sometimes discouraging immunisation if the child had experienced measles already, contrary to DHSS guidelines.[17]

Of the 174 parents interviewed, 43 (25%) were recorded by the computer as not having taken up measles immunisation for their child and 40 of the latter were interviewed or their whereabouts ascertained A small number (nine) said their child had received the immunisation but always after 17 months. Another group (11) had moved out of the area, although the date of the move was unknown. Of the remaining 20 eligible children, seven parents said that they had decided not to take up the immunisation. This was mainly attributed to the child having experienced measles already (three cases) and worries about contraindications as a result of the family or the child's medical history. The other 13 parents said they were 'delaying' immunisation, this was mainly ascribed to their child having another illness—in six cases colds or ear infections—but parents also mentioned previous experience of measles (two cases), worries about possible contraindications, and in a few cases 'forgetting' or 'being too busy.' Few health service problems were mentioned

The uptake of immunisation at 20 months, recorded by the computer system, was 74% for the interviewed group (129/174) and excluding the children who had moved 79% (129/163); 56·5% for the non-responders (13/23); and 73% for the control group (241/330). The immunisation status was unknown in 12 cases. Revised rates of immunisation uptake were calculated from information from the follow up interviews plus the computer records and were 80% (140/174) or 86% (140/163) excluding the children who had moved. The potential uptake figure was based on children known to have been immunised, plus the 13 'delayers' and the three children who were not immunised because of having had measles already; this gave a potential uptake rate of 90% (156/174) and excluding the children who had moved 96% (156/163). If children with other recorded contraindications were included the figures were 92% and 98%, respectively. Actual uptake rates were lower among children whose mothers finished full time education at age 16 or less (68% *v* 83%) or who were from manual social classes (69% *v* 80%), but uptake was higher among first babies (81% *v* 70%); these differences, however, were not quite significant at the 5% level.

### PROFESSIONALS' ATTITUDES

The response rate from all doctors in the two health authorities was 59% (161/274) and that from health visitors was 76% (70/92); professional status was not recorded in five responses. In general there was considerable variation in responses to the recommendations for immunisation between doctors, health visitors, and the two districts. The response rates for the 10 recommendations that were most contrary to what would be expected (based on DHSS guidelines) are summarised in rank order (based on the range of rates) in table 2.

## Discussion

Previous studies of reasons for non-uptake of measles immunisation have been limited by small samples, very local populations, or examination of individual aspects of measles immunisation. In this paper we summarised the findings of a comprehensive range of studies and investigated several aspects of measles immunisation in the same geographical area with random samples of whole district populations We were particularly impressed by the finding that three very different studies, investigating different aspects of immunisation uptake, identified a similar range of problems—for example, all three studies indicated that perceived contraindications to immunisation were an important reason for non-uptake. Further investigation has shown, however, that the contraindications quoted were not valid in most cases. All three studies have indicated that a history of measles was perceived as an important contraindication, although in many cases the disease was a consequence of non-uptake of immunisation and occurred after 15 months of age. Apart from these common problems the individual studies have identified specific problems and several recommendations are made for changes in services based on these findings.

The study on information systems identified several problems in information transfer that could be investigated locally. Potential deficiencies in information transfer that applied to unimmunised children might also apply to immunised children. Hence a comparison of the two groups was carried out. Potential deficiencies identified among the

Table 2 *Proportion of doctors and health visitors who made recommendations for immunisation contrary to those expected based on DHSS guidelines*

| *Case history at age 15 months* | *Response expected (DHSS)* | *Response actually made* | *Doctors (no (%)) (n=161)* | *Health visitors (no (%)) (n=70)* |
|---|---|---|---|---|
| Non-anaphylactoic allergy to egg or milk | Yes | No | 79 (49) | 19 (27) |
| Professional thinks baby has had measles | Yes | No | 86 (53) | 6 (8) |
| Febrile convulsion at age 11 months | Yes/Qualified | No | 48 (30) | 24 (34) |
| Afebrile but snuffly | Yes | No | 51 (32) | 20 (29) |
| Spina bifida and hydrocephalus | Yes | No | 40 (25) | 17 (24) |
| Parent says baby has had measles | Yes | No | 46 (29) | 4 (6) |
| Leukaemia | No | Yes/Qualified | 28 (17) | 10 (14) |
| Irritable/cyanosis when newborn | Yes/Qualified | No | 21 (13) | 14 (20) |
| Meningitis without fits | Yes | No | 23 (14) | 12 (17) |
| Brother has febrile convulsions | Yes | No | 18 (11) | 15 (21) |

unimmunised, however, could still be the true cause of non-uptake. Even if all these barriers to immunisation were appropriately tackled the potential improvement in uptake rate quoted is unlikely to be achieved completely. Several areas for improvement, however, have been identified. families' address changes should be notified by clinics and general pratitioners more promptly and more complete notification of immunisation is required from them. Feedback of uptake rates to general practitioners and health visitors and of lists of apparent 'defaulters' could also help. Children who have not completed the course of triple vaccines should not be suspended from the list for scheduling appointments for measles immunisation; this has in fact been implemented in the national child health computer system. Data on moves in and out of a district and when they occur are necessary to estimate uptake 'Movers out' should not be deleted from the computer file, as is the current practice, but data on the date of their move should be collected and they should contribute to the numerator and denominator of the uptake rate until the time of their move.[18] Finally, those parents who positively withdrew their consent for measles immunisation at the time when it was due (37% of our unimmunised group) could be counselled more positively by health professionals.

In the study on parental attitudes there was no difference in uptake rates between the study and control group (that is, the interview had no effect on the uptake). but there was a difference between responders and non-responders. These uptake rates should be borne in mind when interpreting the results. The non-responding group might have had less favourable attitudes towards measles immunisation and this might also lower the actual and estimated potential uptake rates of measles immunisation. It is clear from the responses that parents differentiated between measles and other immunisations Concern about the side effects of measles immunisation mainly took the form of raising questions about possible side effects rather than actual knowledge or real worries about side effects. It should be noted that the measles questions were asked at 13 months—that is, before the measles immunisation but after the other immunisations were due. Not all babies, however, were first born and some parents should have already been exposed to information on measles. Parents require more advice about measles disease and immunisation from health professionals and more advice about the recognised contraindications for measles immunisation.

We found that the social class distribution of our sample was almost identical with that for married men aged 20–44 in Great Britain in 1980, according to the Registrar General's 1980 social class classification.[19] Differences in uptake rates between socioeconomic groups, although not significant, followed the usual pattern with lower uptake among the manual classes. Such differences may be even greater in areas with a higher proportion of the population in the most disadvantaged groups.

In the study on professionals' attitudes the difference in knowledge and attitudes between doctors and health visitors may actually be greater than observed: the non-responding doctors may have less favourable attitudes than those responding. A small core of professionals have negative attitudes and behaviour towards measles immunisation[16] and there is a larger group whose interpretation of contraindications is at variance with DHSS guidelines.[17] The question with the most variable response was the one on egg allergies. Vaccination is only contraindicated where there is a history of an anaphylactoid reaction, yet 49% (79/161) of the doctors said they would not recommend immunisation with a history of a non-anaphylactoid reaction to eggs. For some conditions—for example, spina bifida and hydrocephalus—measles immunisation is actually indicated because of the adverse effects of measles if contracted by the compromised host. Yet 25–45% of professionals responded 'no' or 'not known' for such cases. Children with a history of convulsions should still be given measles vaccine with appropriate precautions. Yet for the baby that had a febrile convulsion at the age of 11 months, 25–42% of professionals said they would not recommend immunisation. Serological studies in children with a history of measles in early life have shown that a diagnosis in children under the age of 24 months was incorrect in a large proportion of cases; thus immunisation was not contraindicated.[20] A large proportion of doctors in both districts, however, saw a history of measles as a contraindication, particularly if they had made the diagnosis themselves. It should be made quite clear to health professionals that this is not a contraindication.

Health professionals need clearer guidelines on contraindications with periodic reminders. In Maidstone a summary report containing the findings of the study on professionals' attitudes has been distributed to and discussed with health professionals and the department of community medicine has carried out personal communication with individual general practitioners. The department of community medicine at St Thomas's has developed an interactive, computer aided educational program on a BBC microcomputer. The program replicates the professionals' questionnaire, allocates a score based on responses to questions, quotes some of the results of this study, and gives information on DHSS and other guidelines in the feedback to the user. This program may be extended to cover other immunisations. Health visitors can play an important part in monitoring uptake and ensuring that those who 'delay' because of illness eventually take up the vaccine. A questionnaire similar to the follow up interview in the survey on parental attitudes might be used for the purpose of monitoring and audit.

The various calculations of potential uptake of immunisation indicate that a target uptake of 90% is feasible in Maidstone and practical recommendations for service change have been identified. In Maidstone some of these changes have already been implemented and will be supplemented by more aggressive monitoring of non-uptake using the follow up questionnaire. The problems identified in Maidstone probably apply to other districts, and implementation of some of the key recommendations could help achieve the national target of 90% uptake by 1990.

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# Transient protein losing enteropathy associated with acute gastritis and campylobacter pylori

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SUMMARY Three children presented with acute protein losing enteropathy and were found to have acute gastritis associated with *Campylobacter pylori* infection. Recovery from protein losing enteropathy was accompanied by resolution of the gastritis and the disappearance of *C pylori* from the gastric mucosa. Their clinical course suggested that the *C pylori* had caused the gastritis and the protein losing enteropathy. The association between gastritis caused by *C pylori* and protein losing enteropathy in children has not to our knowledge been previously described.

Organisms resembling campylobacter have been reported in association with active chronic gastritis and gastric and duodenal ulcers in adults.[1 2] Recently this association was described in children with symptomatic gastritis.[3] As these organisms are rarely found in normal gastric mucosa it has been suggested they may be the cause of the inflammatory changes.[3 4]

This report describes three children presenting over a period of four months with acute protein losing enteropathy. They were found to have an acute gastritis associated with *Campylobacter pylori*. Recovery from the protein losing enteropathy was accompanied by a return to normal of the gastric mucosa and disappearance of the organisms.

## Case reports

### CASE 1

A 4½ year old girl presented with a week's history of periorbital swelling and pitting oedema of her legs and sacrum. The rest of the clinical examination yielded normal results and she had no skin changes or other features of malnutrition. Her serum protein concentration was 35 g/l and serum albumin concentration 17 g/l. Microscopy and culture of her stool specimen did not show any parasites or bacterial pathogens. A $^{51}$Cr labelled albumin study confirmed protein losing enteropathy; in a four day stool collection 6·2% of the injected isotope was recovered (normal <1%). At gastroscopy swollen gastric rugae were seen with pronounced hyperaemia of the mucosa in the body and (to a lesser extent) in the antrum of the stomach. The duodenum was macroscopically normal. Biopsy specimens of gastric mucosa showed oedema of the lamina propria with an increased number of inflammatory cells that were mainly plasma cells and

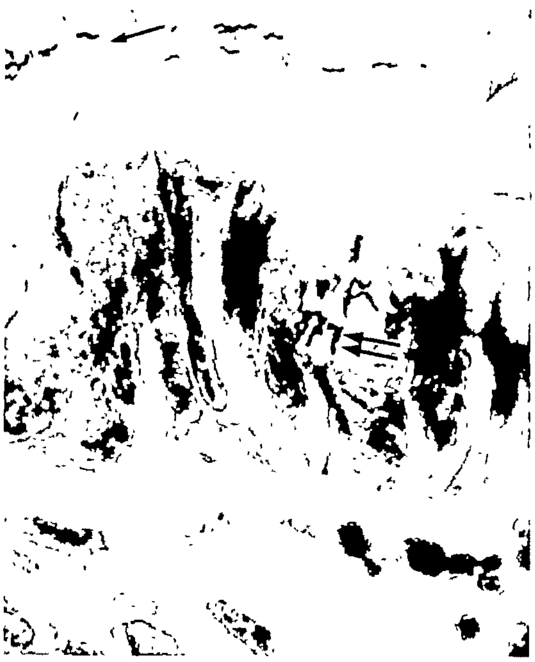

Fig 1 *Gastric mucosal biopsy specimen showing numerous C pylori in superficial mucus (single arrow) and penetrating between cells (double arrow) (Warthin-Starry stain)*

lymphocytes Histology of the duodenal biopsy specimen showed only a slight increase in the number of plasma cells Fig 1 shows that numerous organisms resembling campylobacter were found on the surface of the gastric mucosa on Warthin-Starry staining These were confirmed by electron microscopy to be *C pylori* (fig 2). She was given antacids for the gastritis but no other treatment. The oedema gradually resolved and her serum protein concentration rose, 19 days after admission her serum protein concentration was 53 g/l and that of albumin 27 g/l. Gastroscopy was repeated and showed a macroscopically normal gastric mucosa; histology of biopsy specimens showed a residual mild inflammatory cell infiltrate with scanty organisms resembling campylobacter on Warthin-Starry staining. Culture of a biopsy specimen grew *C pylori*. Two months after admission she had completely recovered and her serum protein concentrations were normal The gastric mucosa was normal both macroscopically and histologically *Campylobacter* could neither be seen on staining nor grown on culture

CASE 2

A boy aged 2 years and 3 months presented with a history of a self limiting episode of diarrhoea two weeks previously that had been followed one week later by generalised swelling. On admission he had pitting oedema of his legs and sacrum, and ascites. He had no skin changes or clinical features of malnutrition and the remainder of the examination yielded normal results Microscopy and culture of a stool specimen did not show any parasites or bacterial pathogens. His serum protein concentration was 28 g/l and serum albumin concentration 10 g/l Protein losing enteropathy was confirmed, as 7·8% of injected $^{51}$Cr labelled albumin was recovered

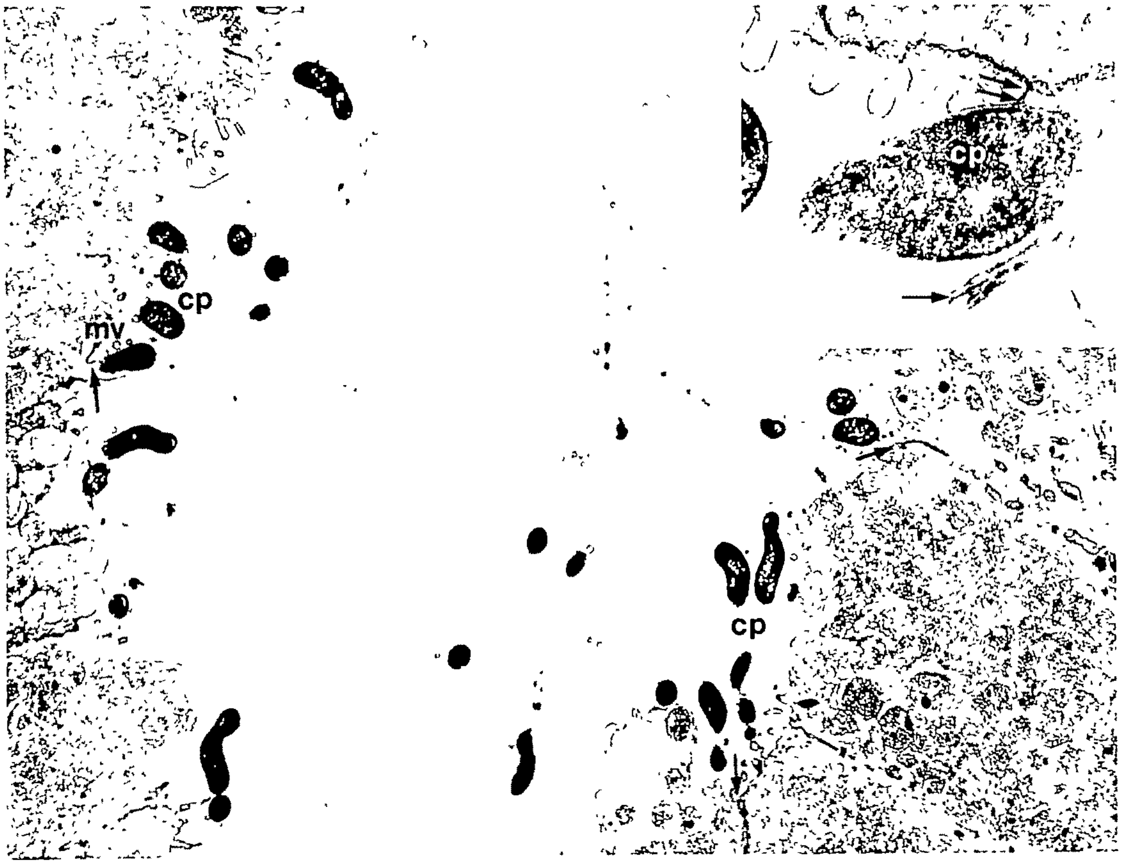

Fig 2 *Low power electron micrograph showing numerous C pylori (cp) in contact with cell membranes and microvilli (mv) and concentrated at intercellular tight junctions (arrows). Inset high power view of C pylori showing characteristic sheathed flagellae (arrow) and association with intercellular junction (double arrow).*

from a four day stool collection. At gastroscopy pronounced hyperaemia of the mucosa of the body of the stomach was found, the antrum being normal. The duodenum also looked normal Histology of the gastric biopsy specimens showed oedema of the lamina propria with an increased number of plasma cells, lymphocytes, and neutrophils On Warthin-Starry staining numerous organisms resembling campylobacter could be seen on the mucosal surface, and electron microscopy confirmed these as *C pylori*. Culture of a gastric biopsy specimen failed to grow the organism He was treated with erythromycin and within 48 hours the oedema began to subside. After 10 days of treatment with erythromycin the oedema had completely resolved and his serum protein concentration was 72 g/l, that of albumin being 39 g/l. Gastroscopy showed normal gastric and duodenal mucosa Histology of biopsy specimens of the body of the stomach was normal, and no organisms resembling campylobacter were detected on Warthin-Starry staining. Culture of the biopsy specimen produced a scanty growth of *C pylori*.

CASE 3

A 3 year old boy presented with a one week history of diarrhoea and generalised swelling for one day. He seemed well nourished but had periorbital swelling and pitting oedema of his legs and sacrum. The rest of the clinical examination yielded normal results. By the time he was admitted to hospital his diarrhoea had resolved and a stool specimen sent for microscopy and culture did not show any parasites or bacterial pathogens. His serum protein concentration was 26 g/l and albumin concentration 12 g/l Protein losing enteropathy was confirmed by recovery of 8·4% of the injected $^{51}$Cr labelled albumin from a four day stool collection At gastroscopy swollen gastric rugal folds were seen and there was intense hyperaemia of the mucosa of the body of the stomach. The duodenum was macroscopically normal. Histology of gastric biopsy specimens showed oedema of the lamina propria with increased plasma cells and lymphocytes. The duodenal biopsy specimen showed only a slight increase in the number of chronic inflammatory cells in the lamina propria. On Warthin-Starry staining numerous organisms resembling campylobacter were seen along the surface of the gastric mucosa Electron microscopy and culture confirmed these to be *C pylori*. He was treated with erythromycin and improved considerably The oedema resolved within three days and by 10 days his total serum protein concentration was 66 g/l, that of albumin being 33 g/l. Gastroscopy at this time showed normal appearances both macroscopically and histologically, and no organisms resembling campylobacter were seen on Warthin-Starry stain. Culture of biopsy specimens from the body of the stomach did not grow *C pylori*.

## Methods

At least eight gastric biopsy specimens were taken under direct vision through the gastroscope on each occasion. Specimens for light microscopy were immediately fixed in Carson's fluid and sections subsequently stained with haematoxylin and eosin and by the Warthin-Starry method. Specimens for electron microscopic examination were fixed in 4% S-collidine buffered gluteraldehyde (pH 7·2–7·4), washed in S-collidine buffer (0·1 M), fixed again in 1% S-collidine buffered osmium tetroxide (pH 7·4), block stained with uranyl acetate, dehydrated in graded alcohols, and embedded in Spurr's resin. Ultrathin sections were stained with uranyl acetate and lead citrate and viewed in a Phillips 201 electron microscope.

Specimens for culture were placed in sterile tubes and taken to the laboratory immediately. Fresh biopsy specimens were moistened with tryptic soy broth and rubbed over the surface of plates of tryptose blood agar base (CM 233, Oxoid Ltd, Basingstoke, Hants, United Kingdom) containing unlysed horse blood 7% v/v. The plates were incubated in a microaerophilic environment at 37°C for up to six days in both a Carbon-dioxide incubator and a Gaspak system (BR 56, Oxoid). The organisms were identified as *C pylori* by their morphological appearances and using accepted biochemical criteria.[5]

## Discussion

These patients all had severe hyproproteinaemia due to protein losing enteropathy that was confirmed by the amount of $^{51}$Cr labelled albumin excreted in the stools There are many causes of protein losing enteropathy in childhood but the history, age, and manner of presentation of these children suggested the diagnosis of Menetrier's disease (giant hypertrophic gastritis). This is characterised by giant gastric rugal hypertrophy seen on barium swallow examination or at gastroscopy [6] There are typical histological features in the biopsy specimens and usually peripheral eosinophilia as well.[6] The cause of Menetrier's disease is uncertain but it may be due to infections with certain viruses such as cytomegalovirus.[7]

The gastroscopic and histological findings in these patients were unlike those described in Menetrier's disease. None had peripheral eosinophilia and no intranuclear inclusion bodies suggestive of cytomegalovirus were seen. Although there was some oedema of the gastric folds, the most striking feature was a severe acute gastritis predominantly affecting the body of the stomach. This contrasts with reports in adults in whom the antrum of the stomach is usually the worst affected. The duodenum was macroscopically and histologically normal in all cases. Histological examination of biopsy specimens of gastric mucosa confirmed the macroscopic appearances of acute gastritis. All had oedema of the lamina propria with increased numbers of inflammatory cells, mainly plasma cells and lymphocytes. Neutrophil polymorphs were prominent in one case and none had eosinophils. Examination by light microscopy showed numerous organisms resembling campylobacter, easily seen using the Warthin-Starry stain, on the surface of the gastric mucosa. The organisms were short, thick 'sea-gull' shaped spiral rods (fig 1). They were lying free in the superficial mucus or attached horizontally to the surface of the gastric mucosal cells where they were often so numerous that they seemed to form a lining sheet. They were also lying between epithelial cells, both surface and glandular, having penetrated the intercellular spaces.

Organisms resembling campylobacter found on examination by light microscopy may be identified as *C pylori* either by recognising the characteristic morphology and sheathed terminal flagellae on electron microscopy[8] or by bacterial culture.[5] All three patients had *C pylori* identified by one or both of these methods. The initial negative culture in Case 2 was probably due to technical problems in the culture method.

Clustering of the *C pylori* around the tight

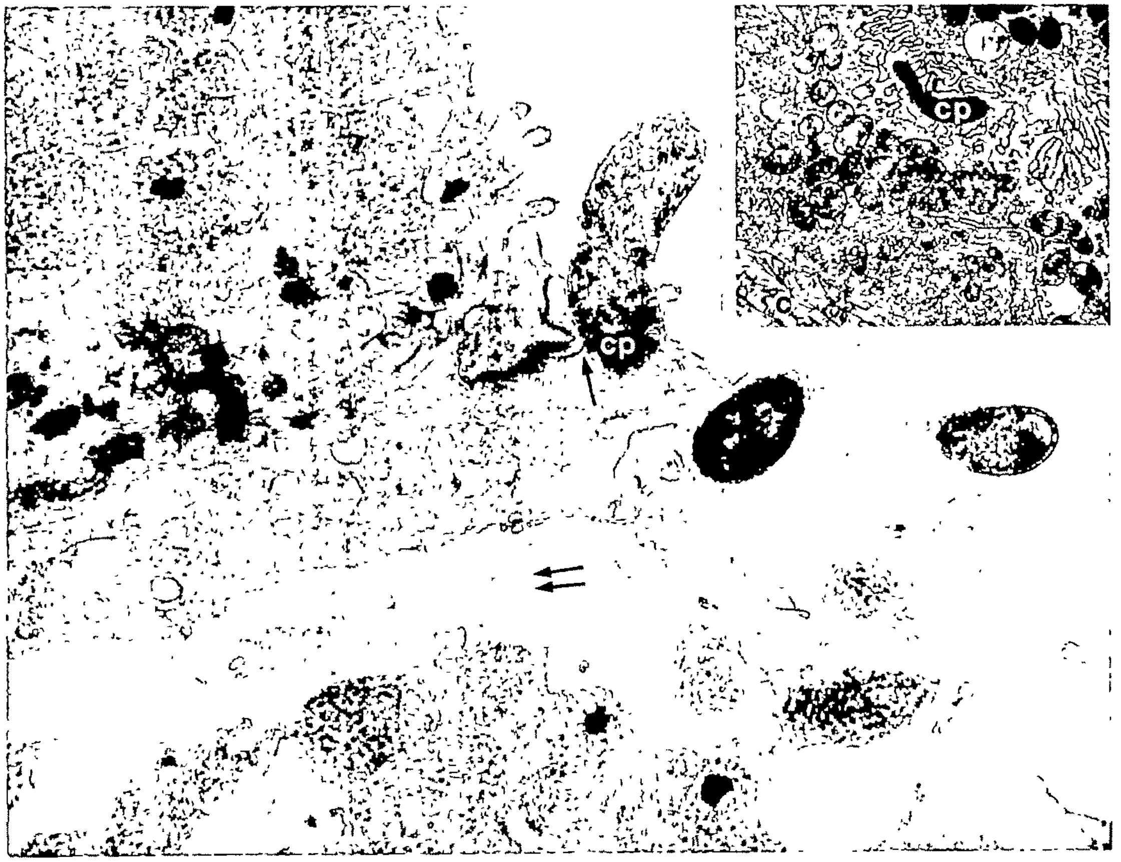

Fig 3 *High power electron micrograph showing C pylori embedded in cell junction (arrow) Second organism is associated with disrupted and widely separated intercellular space (double arrows) containing amorphous material streaming into the lumen of the stomach. Inset: C pylori that has penetrated to base of parietal cell canaliculus; C=subepithelial collagen.*

junctions between the cells was noted on electron microscopic examination Concentration of the organisms in this area has been described previously, and it was postulated that this represented the site through which preferred metabolites and growth factors diffuse [9] In all three cases electron microscopic examination showed that some cells were clearly separated from each other with amorphous material lying in the widened space (fig 3). In addition to disruption of the intercellular junctions, there was cellular degeneration with nuclear pyknosis, increased lysosomal activity, and loss of cell membranes. This disruption of the cellular structure could be the site of the protein loss.

The association between organisms resembling campylobacter and symptomatic gastritis is well known in adults[1 2] and has been described more recently in children.[3] The additional finding of an acute, severe protein losing enteropathy with this association, however, has not to our knowledge been previously reported. It has been postulated that the organisms are the cause of the gastritis as they are not usually found in normal gastric mucosa.[3 4] In addition, clearance of the organisms from the gastric mucosa led to improvement of the gastritis in a series of adult patients.[10] The findings in our patients are in keeping with this, and also suggest that protein losing enteropathy may be a consequence of the gastritis. In each case recovery from the protein losing enteropathy was accompanied by a return to normal of the gastric histology and disappearance of the organisms. In view of the transient nature of the illness and negative clinical findings on admission it is unlikely that any of the other known causes of protein losing enteropathy in childhood were responsible for the disease in these patients. Case 1 was not given antibiotics, and complete recovery from the protein losing enteropathy and gastritis and eradication of the organisms took a long time. In contrast, cases 2 and 3 were treated with erythromycin to which *C pylori* has been shown to be sensitive in vitro[11] and they recovered rapidly in all respects within 10 days. The apparent response to treatment may have been coincidental as others have not found *C pylori* to be sensitive to erythromycin in vivo.[10]

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# Haemophilus influenzae meningitis in Sweden 1981–1983

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SUMMARY Four hundred and seventy cases of meningitis caused by *Haemophilus influenzae* in children and 30 cases in adults were identified in Sweden between 1981 and 1983. The age specific incidence in the most susceptible age group (0–4 years) was 31/100 000/year (440 cases), which is higher than previously reported from Europe. A further 30 cases were seen in children aged 5–14. The risk of developing *H influenzae* meningitis before the age of 15 was 1 in 669. There were 11 deaths (2%) and five cases of serious neurological sequelae among the children. Only 18 children (4%) had predisposing diseases. All but one of the 294 strains of *H influenzae* from children that had been serotyped were type b. Infections in adults differed from infections in children. Five of the adults died (17%) 12 had important predisposing diseases, and at least six of the infections were caused by non-typable strains It is concluded that research into the prevention of invasive *H influenzae* infections in children should have high priority.

The incidence of *Haemophilus influenzae* meningitis in children aged less than 5 years has been comprehensively studied in the United States. The age specific incidence in this group varied between 19 and 71/100 000/year in the general population,[1–3] but three groups of native Americans had high incidences 173–409/100 000/year.[1 4 5] The variations in incidence can be explained partly by racial and socioeconomic differences.

In contrast, little is known about the incidence of *H influenzae* meningitis in children outside North America. Two studies from England reported incidences in children less than 5 years old of only 11 and 18/100 000/year, respectively.[6 7] In The Netherlands,[8] Finland,[9] and a region of Sweden,[10] the incidences were 22, 27 and 27/100 000/year, respectively, in the same age group.

Even though most *H influenzae* infections occur in young children, several recent reports have shown that the organism may also be the cause of meningitis in older children and adults [7 9 11–13] The present study aimed to estimate the incidence and mortality of *H influenzae* meningitis in children and adults in Sweden.

## Patients and methods

We attempted to identify all Swedish residents who had *H influenzae* meningitis between 1 January 1981 and 31 December 1983. All departments of paediatrics, infectious diseases, internal medicine, and neurosurgery in Sweden were contacted about patients with *H influenzae* meningitis. Case records of these patients were examined by the authors at hospitals covering more than 20% of the population The information from the remaining hospitals was obtained from the respective clinicians; 482 patients with *H influenzae* meningitis were identified

Letters were then sent to all departments of clinical bacteriology and to the National Bacteriological Laboratory requesting that all patients in whom *H influenzae* had been isolated from cerebrospinal fluid should be reported to us. Because some laboratories had not kept complete records for the period being studied, this search yielded only 360 patients, 17 of whom had not been found through the hospital search. Their case records were also examined. The departments of medicolegal medicine, where patients who die outside hospital have necropsies carried out, reported an additional patient with *H influenzae* meningitis. Thus a total of 500 cases were found in 498 patients, as two patients had the disease twice at intervals of one and eight months, respectively These episodes have been counted separately.

In 490 cases the diagnosis was confirmed by isolation of *H influenzae* from cerebrospinal fluid and in one case by isolation of *H influenzae* from the meninges and several other organs at necropsy. The remaining nine patients all had clinical meningitis and the cerebrospinal fluid was purulent. *H influenzae* was isolated from blood in eight cases. From one, *H influenzae* type b capsular antigen was detected in the cerebrospinal fluid by coagglutination and Gram negative rods were seen on microscopy of the cerebrospinal fluid.

Four of the adult patients described here have been included in a previous report [11] Sweden has three regions, one in the south with 12 counties, one in the middle with seven counties, and one in the north with five counties. Population data from the 24 counties were obtained from official statistics.[14]

## Results

### CHILDREN 14 YEARS OLD AND UNDER

The age distribution of the 470 patients who were 14 years old or younger is shown in table 1. Of the 470, 440 children (94%) were younger than 5 years old, 272 (58%) were younger than 18 months, and 17 (4%) were younger than 3 months. There were 252 boys (54%) and 218 girls (46%).

The age specific incidence in five year intervals is shown in table 2. The incidence in the most susceptible age group (0–4 years) was 31/100 000/year. The incidences in the southern, middle, and northern regions of Sweden were 27, 37, and 27/100 000/year, respectively. The incidences in the two counties with the biggest cities—Stockholm and Göteborg—were 32 and 24/100 000/year, respectively.

Table 1 *Age distribution related to seroptype of isolate in 500 cases of H influenzae meningitis*

| *Age* | *Type b* | *Type f* | *Non-typable* | *Unknown* | *Total* |
|---|---|---|---|---|---|
| Months. | | | | | |
| 0–2 | 8 | 0 | 0 | 9 | 17 |
| 3–5 | 33 | 0 | 0 | 22 | 55 |
| 6–8 | 42 | 1 | 0 | 28 | 71 |
| 9–11 | 46 | 0 | 0 | 13 | 59 |
| 12–14 | 23 | 0 | 0 | 15 | 38 |
| 15–17 | 22 | 0 | 0 | 10 | 32 |
| 18–20 | 18 | 0 | 0 | 9 | 27 |
| 21–23 | 16 | 0 | 0 | 10 | 26 |
| Years: | | | | | |
| 2 | 39 | 0 | 0 | 24 | 63 |
| 3 | 19 | 0 | 0 | 19 | 38 |
| 4 | 7 | 0 | 0 | 7 | 14 |
| 5 | 7 | 0 | 0 | 2 | 9 |
| 6 | 4 | 0 | 0 | 4 | 8 |
| 7 | 1 | 0 | 0 | 1 | 2 |
| 8 | 2 | 0 | 0 | 2 | 4 |
| 9 | 3 | 0 | 0 | 0 | 3 |
| 10–14 | 3 | 0 | 0 | 1 | 4 |
| 15–19 | 3 | 0 | 0 | 1 | 4 |
| 20–29 | 2 | 0 | 0 | 1 | 3 |
| 30–39 | 4 | 1 | 2 | 0 | 7 |
| 40–49 | 1 | 0 | 1 | 1 | 3 |
| 50–59 | 1 | 1 | 0 | 1 | 3 |
| 60–69 | 1 | 0 | 1 | 3 | 5 |
| 70–79 | 1 | 0 | 1 | 2 | 4 |
| 80–89 | 0 | 0 | 1 | 0 | 1 |

Serotyping of the infecting organism was performed by latex agglutination or coagglutination in 294 of the cases in children (63%) All strains but one were type b; *H influenzae* type f was isolated from a child aged 6 months with no known predisposing diseases. The serotypes of the isolates from the two children with two episodes of *H influenzae* meningitis were not known.

Only 18 children (4%) had any predisposing disease: congenital brain disease (n=10), traumatic head injury (n=4), Down's syndrome (n=3), and malignant lymphoma (n=1). One infant aged 3 months had been born at a gestational age of 30 weeks. All 17 infants aged 0–2 months were born at gestational ages of 37 weeks or more. Only one had a predisposing disease (encephalocele), and this child had a second attack of *H influenzae* meningitis eight months later.

Eleven children (including two neonates) with no known underlying diseases died. Five children developed serious neurological sequelae, such as hemiplegia, diplegia, or tetraplegia, in combination with mental retardation, blindness, or epilepsy. The mean time spent in hospital was 12 days.

### PATIENTS 15 YEARS OLD AND OLDER

There were 30 adults (6% of all patients) aged between 17 and 82 years. Eleven were men and 19 women. Their ages and the serotypes of the isolates are shown in table 1. The adults differed from the children in serotype distribution, predisposing diseases, and outcome. Of the 21 strains that were

Table 2 *Age specific incidence (cases/100 000/year) of Haemophilus influenzae meningitis in Sweden 1981–1983.*

| *Age (years)* | *Mean population* | *Documented cases of H influenzae meningitis* | *Age specific incidence* |
|---|---|---|---|
| 0–4 | 477 461 | 440 | 30 7 |
| 5–9 | 530 926 | 26 | 1 6 |
| 10–14 | 563 927 | 4 | 0 2 |
| 0–14 | 1 572 314 | 470 | 10·0 |
| 15 and over | 6 752 610 | 30 | 0·1 |
| Total | 8 324 924 | 500 | 2·0 |

serotyped, only 13 were type b, two were type f, and six were non-typable. Predisposing diseases were known in 12 adults (40%) and comprised head injury (n=11) and acute lymphatic leukaemia (n=1), Five (17%) of the adult patients died. Among those were two patients aged 29 and 36 years with type b infections and no known predisposing disease.

### *β lactamase producing strains*

Twenty nine strains (6%) (from 12 of the 24 counties) produced β lactamase.

## Discussion

Like all previous estimates of the incidence of *H influenzae* meningitis in children[1–10] the results of the present study are based on a retrospective search for patients; the true incidence of *H influenzae* meningitis in Sweden is probably higher than that reported here. Some episodes of meningitis might never have been diagnosed, and some patients might have become ill abroad.

The incidence of *H influenzae* meningitis in children aged 0–4 years in Sweden from 1981–1983 that we report (31/100 000/year) is higher than that previously reported in Europe[6–10]—11-27/100 000/year. The incidence in Europe seems to be similar to or somewhat lower than that reported from white middle class North American populations, and considerably lower than in North American black and American Indian populations.[1–5] The risk of developing *H influenzae* meningitis in Sweden is, according to our data, 1/669 before the age of 15 years.

The impact of invasive *H influenzae* type b disease on morbidity and mortality in children is considerable. The mortality from *H influenzae* meningitis in Sweden is 1–2%.[10] The 11 fatal cases described here comprise 0·4% of all deaths (2822) in children aged 0–14 years during the same time period; the mortality reported from other countries (5–8%) is higher.[5–7]

There were five children with serious neurological sequelae. The prevalence of less severe sequelae could not be estimated in this study, but other studies have described auditory impairment, mental retardation, motor abnormalities, visual impairment, language disorders, and behavioural or psychological problems, alone or in combination, in 27–33% of survivors.[20–22] In addition children who seem to recover completely from meningitis have a lower mean intelligence quotient and perform less well than their siblings at intellectual and neurophysiological tests.[23 24] There are also other manifestations of *H influenzae* infection, notably epiglottitis, which in Sweden seems to be more common than *H influenzae* meningitis,[25] septicaemia, pneumonia, osteitis, and arthritis.

The purified *H influenzae* type b capsular polysaccharide vaccine could only have prevented 31–42% of the cases described here because it is only immunogenic in children over the age of 18 to 24 months.[15 16] The experimental vaccines comprising the *H influenzae* type b polysaccharide conjugated to proteins are of great interest as they will probably induce immunity from the age of 3 months.[17–19]

Although *H influenzae* type b meningitis is mainly a disease of young children, the infection is also seen in adults.[7 11–13] In the present study nine adults aged 17–55 years with no known predisposing diseases had *H influenzae* type b meningitis, indicating that some apparently healthy adults in Sweden lack protective antibodies against *H influenzae* type b. The finding of 17 infants born at term who got *H influenzae* meningitis before the age of 3 months indicates that women of childbearing age in Sweden do not always have protective amounts of *H influenzae* type b antibodies in their blood. There are many differences between *H influenzae* meningitis in children and adults. In adults the disease is more often related to predisposing diseases and the mortality is high[11–13]; in the present study it was 17%. In older patients with predisposing diseases non-typable strains of *H influenzae* are also important pathogens as we have shown both here and previously.[11–13]

In conclusion, research into the prevention of invasive *H influenzae* infections in children by immunisation should have a high priority because of the high incidence, the prevalence of sequelae, and the low but nevertheless important mortality.

We thank all the doctors who identified and provided information about patients with *H influenzae* meningitis and also Jan Persson for help with computer processing of the data.

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# Longitudinal study of height and weight at adolescence

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SUMMARY A longitudinal study through puberty of the height and weight of 96 boys and 102 girls in schools in and around the city of Leeds was conducted. Data for height and weight and height and weight velocities are presented, which are based on chronological age and on age relative to the age of peak height velocity. Comparison was made with the Tanner standards: male puberty developed a little later but growth continued longer, so that the adult men were taller and heavier. Girls showed a similar timing of puberty to the Tanner standards but were lighter at all ages and ultimately slightly taller as growth was not completed until later. It is important to know the pubertal state when interpreting growth changes in children.

In clinical practice much emphasis must be placed on reliable standards of normality in growth. The difficulties of obtaining standards that are up to date and appropriate for populations are very great especially for the years covering adolescence. Nevertheless, there is value in obtaining fresh data from time to time and relating these to previous standards. Twenty years ago Tanner, Whitehouse, and Takaishi produced outstanding papers that contained standards for height and weight, and they have been widely used.[1] The authors emphasised the importance of longitudinal data for adolescence, which is the period when the precise age of growth patterns varies greatly. The present longitudinal study, started in 1973, was undertaken to provide such information on children whose backgrounds were rather different from those reported by Tanner.

## Subjects and methods

A single cohort of white schoolchildren (121 girls, 120 boys), without chronic disease, was recruited from seven day middle schools in and around Leeds. The schools chosen were selected because they would represent a cross section of social backgrounds and because staff support and cooperation could be expected. In response to a brief introductory notice about the proposed project interested parents with children in the appropriate year group (mostly 10 to 11 year olds) were invited to attend meetings at the schools and the full nature of the study was explained. It was emphasised that if a child entered the programme it was hoped that he or she would stay in it, although there was no obligation to do so. It became apparent that when the children progressed into adolescence their own willingness to continue participating lessened and five girls and six boys had to be excluded from the study because they withdrew at this stage. Children also withdrew at various stages of the project because they moved away or changed schools.

At the age of 13 the cohort went from the middle schools to many different high schools; in each of these the number of participants became relatively small and follow up much more difficult. A high proportion of pupils left school at the age of 16 years and though every effort was made to see them subsequently many were lost to follow up. Of those with whom contact was retained most could not continue to be seen at the same four monthly interval. Fortunately, most girls had almost completed their growth by the age of 16 so further follow up was not so crucial, but this was not the case with the boys.

The final analyses included only those children who were seen initially from an age when they were completely prepubertal, or in a small proportion (15 girls, two boys), in the earliest stage of puberty (Tanner stage 2 breast or genital development), and who were followed up until after the age of peak height velocity.[2] Results are therefore presented on 96 boys and 102 girls.

### MEASUREMENTS

Children were measured once a term, as close to four monthly intervals as possible and always within the range of three to six months. Repeat visits were often made to see previous absentees. The children were normally seen in the school 'medical' room. The measurements were made by one of us (JMHB) with the exception of pubertal ratings in the older girls which were evaluated by JW, who also recorded the results alongside previous records. The measurements were done without the observer knowing the previous values but were repeated if an error was suspected.

Height was measured according to the standard method of Tanner *et al* using a Harpenden anthropometer.[3] The subjects were weighed with high quality bathroom scales (Krups, Republic of Ireland); in view of the recognised fluctuations in weight from hour to hour and day to day greater accuracy was regarded as unrealistic.[4] Pubertal ratings were assessed according to the descriptions of Tanner in terms of genital development in boys, breast development in girls, and pubic hair in both sexes.[2] The age of onset of menstruation in girls was recorded. The first sign of puberty in boys was in most instances growth of the testicles to a size of 4 ml or greater (based on comparison with a Prader orchidometer).

### ANALYSIS OF DATA

### *Adjustments for missing or erroneous data*

Repeat visits were made to schools to see previous absentees, but for some of the measurements (76 of 2180 (3%) for boys, 85 of 2179 (4%) for girls) interpolated values were used as it was impossible to obtain measurements within six months of the previous ones. When subjects had left school, observations in many cases were reduced to once a year Those still growing fast were followed up at the same intervals or not included after that age. In a minority (38 girls (37%), 22 boys (23%)) in whom complete follow up was not possible but who (on the basis of constancy of consecutive height measurements when last seen or a rate equal to or less than 1·5 cm over the last year) had clearly already effectively achieved adult stature, these last records for height and weight were extrapolated to the age of 17 years in girls and 18 years in boys.

Review of height measurements subsequently has shown a few values that were clearly mistakes (44 of 4261 (1·03%) for height and 24 of 4261 (0·56%) for weight), and appropriate corrected values have been assumed. In about half the instances corrections for height were only of the order of 2–5 mm. Most of the 'editorial procedures' were similar to those of the Swedish longitudinal study of 1976.[5]

### *Centile distributions*

There was, of course, no uniformity in the actual chronological ages at which measurements were taken. A Fortran computer program was therefore used, which by interpolation between the values at known ages for each individual derived values for all subjects at the same half yearly ages. Thus for height and weight centile distributions could be determined over the age range 10 to 17 years for girls and 10 to 18 years for boys.

Weight and height velocities were calculated on a yearly basis—that is, taking every third measurement and dividing the increase by the exact time interval. The age at which the velocity is reported is midway between these two ages. Thus after the first year it was possible to calculate three velocities per year for each subject. The age of peak height velocity for a child (see below) was taken as the age where the maximum value occurred. Centile distributions of velocities were obtained in a similar manner to height and weight growth curves—that is, for each child velocities at half yearly intervals were interpolated by computer.

Centiles were also produced where the age axis was defined as age relative to age at peak height velocity. For each subject the age of peak height was determined as described above. Velocities were obtained by interpolation at half yearly intervals relative to this point.

Table 1 *Duration of follow up measurements*

| *Mean (SD) age when first seen* | *No (%) completely prepubertal when first seen* | *Duration of follow up in years (SD)* | *No (%) seen through the age of PHV** | *No (%) seen past the age of menarche* | *No (%) seen until fully grown* |
|---|---|---|---|---|---|
| | | *Boys (n=96)* | | | |
| 10·10 (0·71) | 92 (96) | 7·08 (1·31) | 96 (100) | | 54 (56) |
| | | *Girls (n=102)* | | | |
| 9·68 (0·66) | 87 (85) | 6·60 (1·59) | 102 (100) | 98 (96) | 69 (68) |

*Peak height velocity

## Results

Over half the children were followed up until they were effectively of adult stature (table 1) and 98 of the 102 girls were past the age of menarche when last seen. The length of follow up is also shown in the table.

Centile curves are shown in figs 1–4. The results are all presented with respect to chronological age and with respect to age relative to the age at peak height velocity. Fig 1 shows the height curves of the boys and girls, fig 2 shows the weight curves, and figs 3 and 4 show the corresponding velocity curves. The spread of the ages over which the various stages of puberty occurred in the present study compared with those of Tanner's data[6] are shown in figs 5 and 6 for boys and girls, respectively.

The figures confirm the well recognised difference

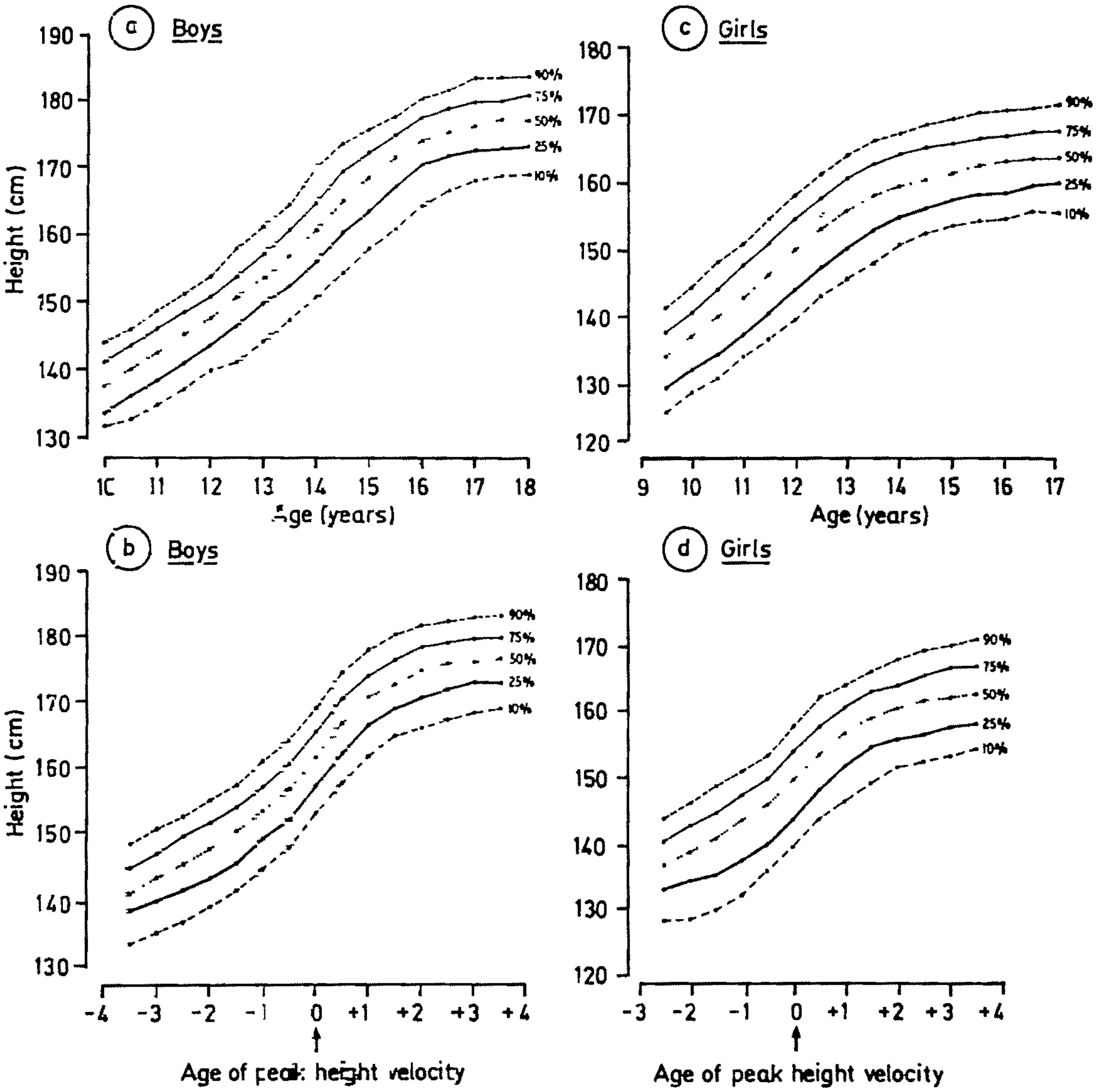

Fig 1 *Centile curves for height for girls and boys, a and c with respect to age and b and d relative to the age of peak height velocity.*

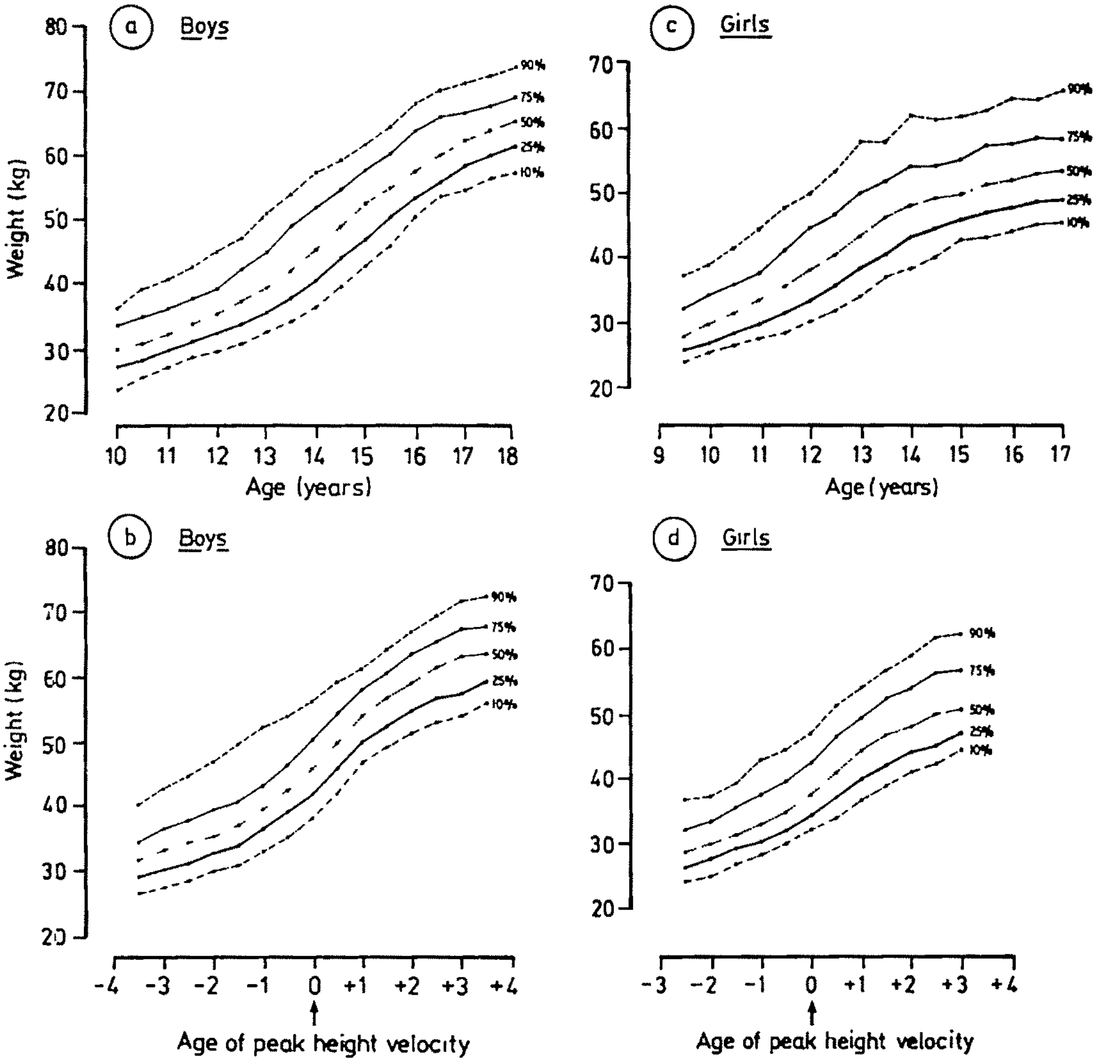

Fig 2 *Centile curves for weight for girls and boys; a and c with respect to age and b and d relative to the age of peak height velocity*

in the way boys and girls grow at puberty. They show that girls develop earlier; for a short period are taller and heavier than boys; and that they slow down and stop growth on average two years before boys who end up on average 14 cm taller and, at age 17, 8 kg heavier. Some of these comparisons between the sexes in terms of age and magnitude of the growth spurts for height and weight are shown in table 2. The age when the average boy was growing at his fastest in height was very close to the age when he was increasing weight most rapidly. Girls, however, seemed to put on weight most rapidly later than the age of their peak height velocity.

## Discussion

The practical difficulties encountered in arranging for one observer to see about 200 children three times a year for several years were vast. There was unavoidable inconsistency in the circumstances of measurement, interval between examination, timing of day, etc, which could influence the results.[7]

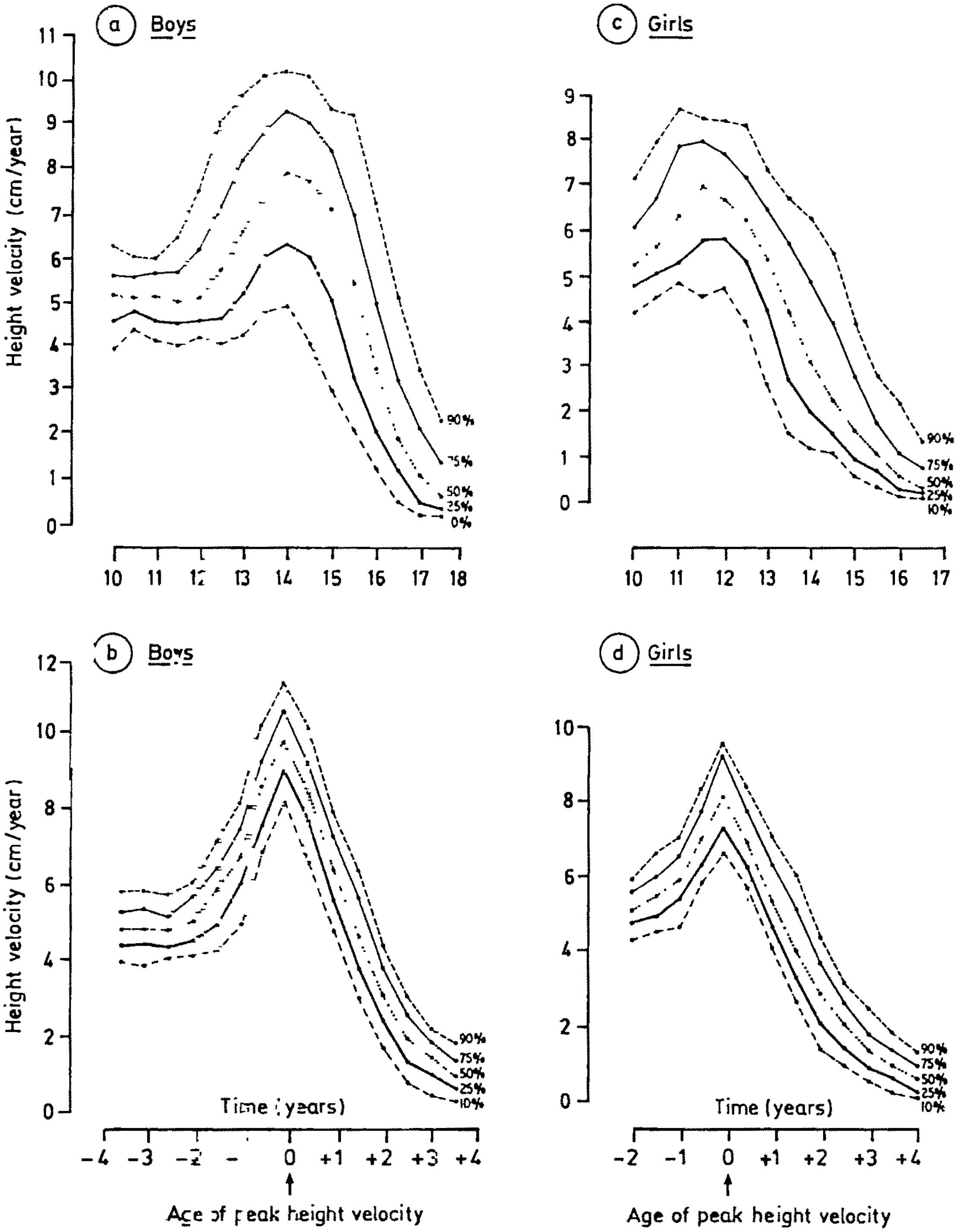

Fig 3 *Centile curves for height velocity for girls and boys, a and c with respect to age and b and d relative to the age of peak height velocity.*

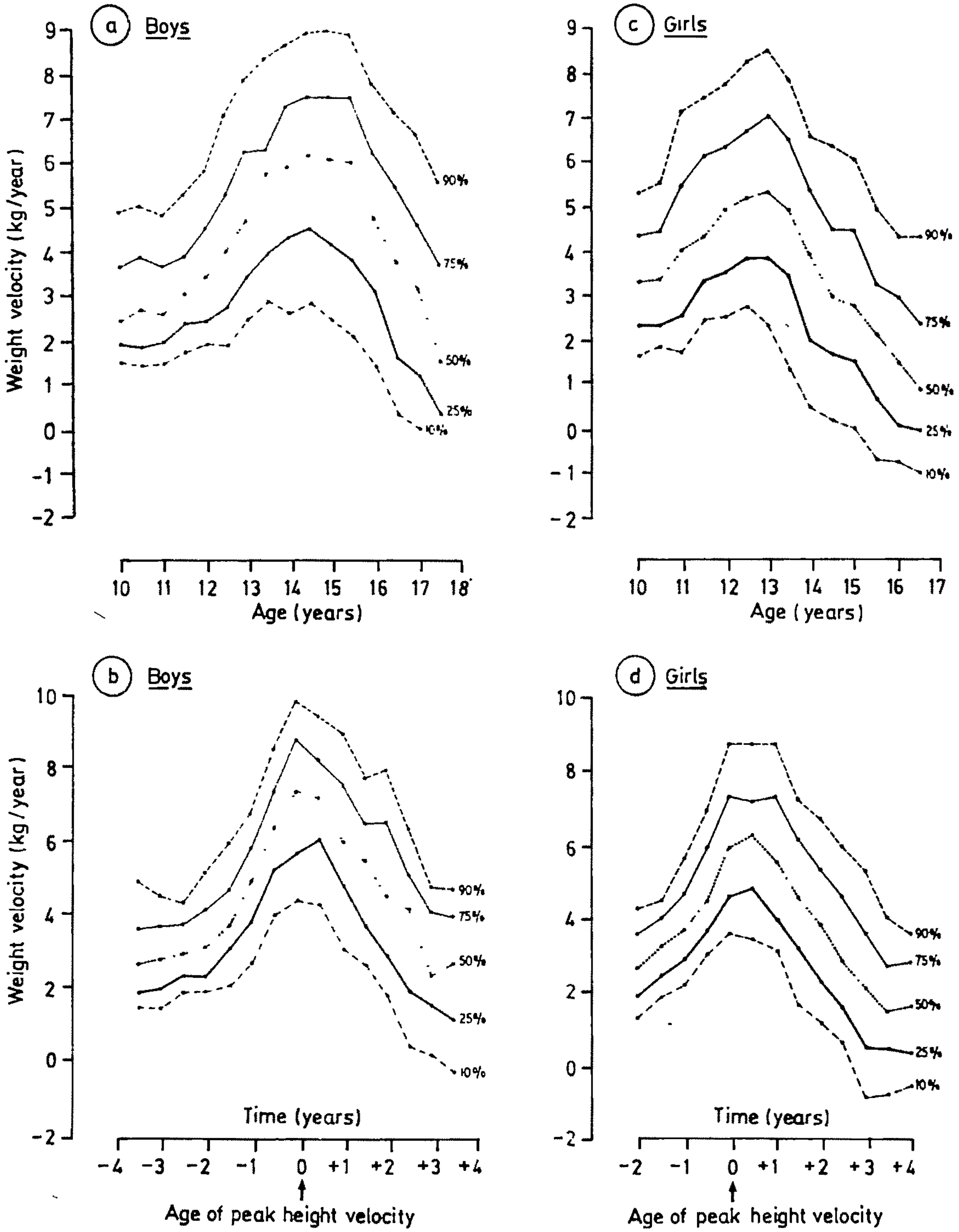

Fig 4 *Centile curves for weight velocity for girls and boys; a and c with respect to age and b and d relative to the age of peak height velocity.*

Interpolated and extrapolated values are not scientifically ideal but were used only as a last resort. Omitting values could have introduced greater errors into the overall statistics.

Subjects were excluded, however, if they did not reach their peak height velocity during the course of the study or if they were beyond Tanner stage 2 breast or genital development when the first measurements were taken. It is arguable that these children represented the extent of the range of normality and should be included to give a true picture. It was nevertheless felt that subjects with such incomplete data should not be included.

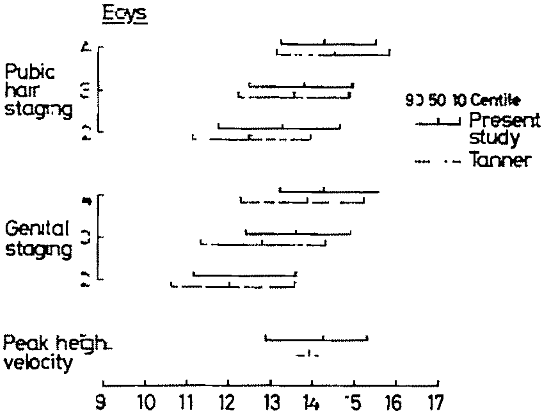

Fig 5 *Ages of the stages of puberty for boys in this study compared with those of Tanner et al.*[13]

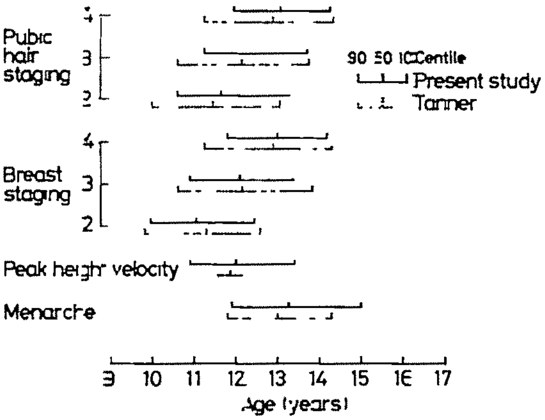

Fig 6 *Ages of stages of puberty for girls in this study compared with those of Tanner et al.*[13]

Centile charts based on chronological age when used on their own can be misleading and some means of including data relevant to pubertal state is of importance. The use of centiles based on peak height velocity related ages not only provided a standard of comparison for the shape of individual distance and velocity curves, but gave a better indication of 'true physiological' centile placement. Age of peak height velocity was defined as the age at which the highest velocity value was obtained. As Preece[8] has reported there are various methods of fitting curves to data—for example, principal components[9] and moving polynomial functions.[10] Our measurements, however, were obtained at roughly four monthly intervals and this therefore sets the limit of our accuracy (whatever method of analysis is used). It would have been possible to calculate four monthly velocities—that is, the velocity between consecutive measurements rather than measurements about a year apart, but although in theory this would identify more precisely the shape of the velocity curve during the time of rapid change in practice it is liable to much greater error resulting from any inaccuracy in measurement or seasonal variation in growth rate.[11]

Although of academic value, the centiles presented, with age expressed relative to age at peak height velocity, are of limited clinical application as the age of peak height velocity is unlikely to have been reached at the relevant time of concern. Even before the age of peak height velocity is reached there can be a guideline by assuming an interval in time between the age of appearance of other pubertal features and peak height velocity. This is clearly approximate, and evidence from these

Table 2 *Magnitude of the growth spurts for height and weight*

| *Peak height velocity* | | | | *Peak weight velocity* | | | |
|---|---|---|---|---|---|---|---|
| *Age in years (SD)* | *Range* | *Magnitude in cm/year (SD)* | *Range* | *Age in years (SD)* | *Range* | *Magnitude in kg/year (SD)* | *Range* |
| | | | | *Boys (n=96)* | | | |
| 14·12 (0·9[illegible]) | 11·89–16·4[illegible] | 9·79 (1·23) | 7·00–13·33 | 14·2[illegible] (0·98) | 12·26–16·47 | 8·64 (1·72) | 4·67–13·67 |
| | | | | *Girls (n=10[illegible])* | | | |
| 11·99 (0·9[illegible]) | 10·07–14·8[illegible] | 8·14 (1·07) | 4·57–10·10 | 12·7[illegible] (1·08) | 10·07–15·80 | 7·81 (1·88) | 4·60–13·78 |

studies and others[12] indicates that the earlier puberty occurs the shorter the time interval between the appearance of a feature of puberty and peak height velocity.

The reports of Tanner *et al* were based mainly on London schoolchildren in 1959 together with longitudinal data of the Harpenden Growth Study completed in the mid 1960s.[1 6 13] Comparisons of our results with these reports was interesting. Puberty in all stages occurred later in the boys in the present study (fig 5). The average age of onset of genital development was 0·5 years later than those in Tanner's study,[6] first appearance of pubic hair about 0·8 years later, and the age of peak height velocity 0·35 years later. (In the report of the Harpenden Study in 1976,[13] however, somewhat different ages were given, pubic hair appearance being later and comparable with the findings of this report, whereas genital development was even earlier being slightly over a year younger than in our boys.) Interpretation of the first stage of genital development in boys (testicular growth) shows great variation from observer to observer and these differences may be misleading.

Differences in the ages of pubertal development in girls were far less pronounced (fig 6). The mean age of peak height velocity is almost identical in the studies and the mean age of menarche, although 0·25 years later than one of Tanner's reports from 1976[6] was almost identical with the age given in another 1976 report.[13] The ages of pubic hair and breast development were comparable.

The growth in height was different from that of the Tanner series in both boys and girls The present group of boys and girls were slightly taller initially, but their final height was definitely taller on average: boys by 2·5 cm, girls by 1·5 cm. This seemed mainly due to the fact that growth had continued longer as the difference was not evident at the stages of more rapid growth.

Weight differences in this study were even more apparent but not in parallel ways in the boys and girls. The boys in this study were a little lighter throughout at comparable ages up to 16, presumably due to changes of puberty being later, and were on average 2 kg lighter at age 15 Ultimately, however, weight gain was greater and by 18 they were about 2 kg heavier on average than those of Tanner's standards. The Leeds girls were lighter at all ages than those in Tanner's study, they were less so prepubertally (averaging 1 kg lighter) but in mid puberty were about 3 kg lighter, and this difference was maintained despite the fact that these girls were ultimately slightly taller.

At school entry between the ages of 5 and 6 Leeds schoolchildren were of comparable height and weight to Tanner's standards.[14] It would seem that differences arise later, primarily related to pubertal growth.

A Swedish study in 1976 showed basically intermediary results between the present study and those of Tanner *et al*[5] There was little difference in the timing of peak height velocity in girls (12·0 years average) or menarche (average 13·0 years), though in boys it was fractionally earlier (14 years in the Swedish series compared with 14·25 years in the present study). The measurements of the Swedish children throughout the age range were slightly greater· boys being about 2 cm taller and 1–2 kg heavier, and girls 1–1·5 cm taller and 3–4 kg heavier than the Leeds children. Values were only reported up to age 16, however, by which time our subjects seemed to be catching up in height and may have ended up taller through continuing to grow for a longer time.

A recent report, comparing French and English children born in 1953, found a lower body mass index in the French children.[15] The present series of Leeds schoolchildren was more in line with the French children in that study. Another study that followed up children born in Newcastle in 1947 reported weights for boys and girls at ages 13, 14, and 15 that were very similar to this report.[16] In terms of stature, however, the Newcastle children were considerably shorter· boys on average by 4·5–5 cm throughout, girls by 5 cm at 13, but about 3·5 cm ultimately, puberty being a little later. Our study shows that adolescent children today have lower values weight for height than in the past.

Tanner and Davies recently produced standards for height (though unfortunately not for weight) for American children showing that in puberty they develop earlier (the peak height velocity for boys averaged 13·5 and for girls 11·5) and so are considerably taller than comparable British 14 year old boys and 12 year old girls.[17] The average ultimate heights, however, for the present series of British boys and girls are about the same as those of the American children.

This paper shows the inevitable difficulties and limitations of longitudinal studies, but such studies are essential to elucidate the growth pattern of children as this is obscured by cross sectional studies. Numbers must of necessity be small if observations are to be consistent, reliable, and performed by a single observer; and the cooperation of the subjects must be maintained When numbers are so small the significance of obtaining extremes of centile values may be questioned and also how representative this group is of the population as a whole. Different social and cultural backgrounds may influence growth patterns and we intend to investigate this further. The most important factor influencing growth in the teenage years, however, is the stage of pubertal development. Centiles based on peak height velocity related ages are therefore particularly useful for this age range.

We thank the staff and pupils of the schools that participated in this project, Mrs Gillian Levell and Mrs Jyoti Anancjiwala for clerical help; Mrs Janet Walsh for typing the manuscript, and Rev W Sollom for devising the computer program and for his encouragement and advice. This study has been supported through the years by grants from the Children's Research Fund, Leeds Teaching Hospitals' Special Trustees Fund, University of Leeds Research Fund, the Child Growth Foundation, and KabiVitrum Ltd

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# Congenital cytomegalovirus infection: a cause of sensorineural hearing loss

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SUMMARY Prospective studies have suggested that about 108 children with congenital cytomegalovirus (CMV) infection and bilateral sensorineural hearing loss are born each year in England and Wales; this represents about 12% of all children with congenital sensorineural hearing loss. Over a nine year period 1644 children aged between 6 months and 4 years who were attending the Nuffield Hearing and Speech Centre were screened for CMV infection. The prevalence of CMV in the urine of children with sensorineural hearing loss but no immediate family history of deafness was nearly twice that (13%) found in other children with impaired hearing and those with normal hearing (7%). These findings indicate the importance of CMV as a cause of hearing loss.

Congenital cytomegalovirus (CMV) infection is the most common congenital infection in the United Kingdom with a prevalence of 3–4/1000 live births.[1-3] Most congenitally infected infants are asymptomatic and the infection is unrecognised, and fewer than 10% present with clinical signs at birth or in the early neonatal period Children with clinical infection have a high risk of handicap that considerably impairs their development.[4-6] In a study of 34 such infants Pass *et al* reported that all surviving children had evidence of damage by CMV with or without impairment of hearing.[5]

Prospective studies of children with congenital CMV infection identified by routine screening in the first few weeks of life have also shown that those with asymptomatic infection may subsequently manifest varying degrees of sensorineural hearing loss.[7-13] Moderate to profound hearing defects, either bilateral or unilateral, have been identified in about 10% of children with congenital CMV infection.[13]

A small number of histological studies of temporal bones of children who died from congenital CMV infection suggests that CMV can cause damage to the inner ear. Myers and Stool reported infected epithelial cells in the walls of the inner ear and stria vascularis with pronounced hydrops of the cochlear duct and saccule,[14] and Davis reported similar results in eight neonates who died of congenital CMV infection.[15] CMV has also been cultured from perilymph,[16] and Stagno *et al* found viral antigen in the spiral ganglion neurones and the organ of Corti.[11] The association with specific ear damage remains obscure and the mechanism whereby virus is transmitted to the inner ear is not known.

Many unexplained cases of sensorineural hearing impairment may be due to subclinical CMV infection and classified as congenital deafness caused by unknown or recessive genetic factors. A diagnosis of congenital CMV infection is only possible if CMV is isolated during the first three weeks of life, or if CMV IgM is found in a sample of serum taken at or shortly after birth. After this time congenital infection cannot be distinguished from acquired infection; this is common in infants[17] and has not been associated with sensorineural hearing loss. Children with congenital and early acquired infection continue to shed virus in their urine for some years.[17 18]

To estimate the part played by CMV in the aetiology of childhood deafness the prevalence of CMV in the urine in children with sensorineural deafness was compared with that among other handicapped groups of children and those with normal hearing.

## Patients and methods

Between January 1972 and December 1980, 1644 children aged between 6 months and 4 years who had been referred to the Nuffield Hearing and Speech Centre were examined for the presence of CMV in the urine. Urine samples were collected in sterile plastic bags or disposable containers. About 2 ml of urine were mixed with an equal volume of virus transport medium containing sorbitol and stored at 4°C before transport to the laboratory in a thermos flask with wet ice on the same day. The samples were then inoculated into cultures of human embryo lung fibroblasts, the period between collection and inoculation rarely being longer than six hours. The cells were examined twice a week for the cytopathic effect of CMV over four weeks. CMV was subsequently confirmed by complement fixation against a standard CMV positive serum.

The medical records of children were examined and the final clinical diagnosis recorded. Each child was assigned to one of the following diagnostic categories: (i) sensorineural hearing loss without a family history of deafness; (ii) sensorineural hearing loss with a family history of deafness; (iii) speech problems but normal hearing; (iv) conductive hearing loss; (v) other conditions—for example; acquired hearing loss, delayed development, structural malformations and syndromes—and; (vi) no abnormal findings

Most of the children with sensorineural hearing loss had bilateral, moderate to profound deafness and hearing aids had been prescribed

Children from whom CMV was isolated between January 1974 and February 1980 were asked to provide a further specimen of urine at each of their subsequent visits. The 60 children positive for CMV who provided a second specimen of urine were matched on the same day with the next child of the same age who did not excrete CMV. Both groups of children were tested at each subsequent visit until December 1981. The clinical details of these 120 children were obtained from their case records and the two groups compared.

Table 1 *Diagnostic categories of children aged 6 months–4 years screened for cytomegalovirus infection 1972–1980*

| | *Total No* | *No (%) of children with CMV in the urine* | |
|---|---|---|---|
| Sensorineural hearing loss without family history of deafness | 623 | 82 | (13·2) |
| Sensorineural hearing loss with family history of deafness | 92 | 5 | (5·4) |
| Speech problems but normal hearing | 334 | 28 | (8·4) |
| Conductive hearing loss | 216 | 15 | (6·9) |
| Other conditions | 165 | 16 | (9·7) |
| No abnormal findings | 214 | 10 | (4·7) |
| Total No | 1644 | 156 | (9·5) |

## Results

CMV was isolated from the urine of 156 of 1644 children (9·5%). For each year during the study period the percentage of children with CMV in the urine varied between 9 and 11. Table 1 shows that nearly twice as many children with sensorineural hearing loss but with no family history of deafness (82 of 623, 13·2%) were shedding CMV, compared with children from the other five diagnostic groups combined (74 of 1021, 7·2%) ($\chi^2=15{\cdot}8$ $p<0{\cdot}001$). The group of children with no abnormal findings had the lowest rate of excretion of CMV.

A more detailed analysis was carried out for the 451 children who were screened between January 1976 and December 31 1980 and who had sensorineural hearing loss (table 2). Evidence suggesting congenital rubella deafness was present in 102 children (23%). In 63 (14%) the diagnosis was considered to be probable in view of the serological findings, clinical signs, and maternal history; in 39 congenital rubella was possible, but the available

Table 2 *Children aged 6 months—4 years with sensorineural hearing loss associated with family history of deafness, congenital rubella, infection, and other conditions 1976–1980*

| | *No of children screened* | *No (%) of children with CMV in the urine* | |
|---|---|---|---|
| History of deafness in immediate family | 47 | 0 | (0) |
| History of deafness in distant relative, often vague | 19 | 4 | (21·0) |
| Congenital rubella probable* | 63 } 102 | 8 } 17 | (12·7) } (16·7) |
| Congenital rubella possible† | 39 | 9 | (23·0) |
| Mental retardation, cerebral palsy or epilepsy | 31 | 3 | (9·7) |
| Deafness following meningitis | 31 | 5 | (13·3) |
| No history of the above conditions | 221 | 34 | (15·4) |
| Total No | 451 | 63 | (14·0) |

*=Rubella antibody in a child ≤3 years old, maternal history of rubella in pregnancy or other congenital rubella defects, or both †Rubella antibody in child aged >3 years, or maternal history of rubella in pregnancy, or both

evidence was insufficient to make the diagnosis. The children with probable congenital rubella had a lower prevalence of CMV excretion than those with a less certain diagnosis, although this was not significant ($\chi^2=1\cdot8$ $p<0\cdot25$). There was, however, a significant difference in the prevalence of CMV excretion between the group of children with a family history of deafness in a first degree relative and the group in which a more distant relative was affected and the family history was vague ($\chi^2=10\cdot5$ $p<0\cdot01$).

FOLLOW UP OF 60 CHILDREN WITH CMV IN THE URINE
The 60 children in whose urine CMV was first identified between 1974 and 1981 provided a further 149 urine samples, and the 60 children who were initially negative for CMV provided a further 144 samples. Specimens were collected at irregular intervals as children only attended the centre when there was a clinical need. The figure shows the age at which the 60 children who were initially positive for CMV were first screened, and the ages at which subsequent specimens were taken

Twenty six children were first tested and found to be shedding virus before their second birthdays and 34 between the ages of 2 and 4 years. Overall, 47 of the 60 children shed virus intermittently—in some cases for more than five years. All but one of 13 children from whom CMV was isolated only on the first occasion were over 2 years old when first screened. In contrast to the children initially positive for CMV, only one of the 60 control children excreted CMV at follow up, and then on only one occasion, although 144 subsequent samples were tested.

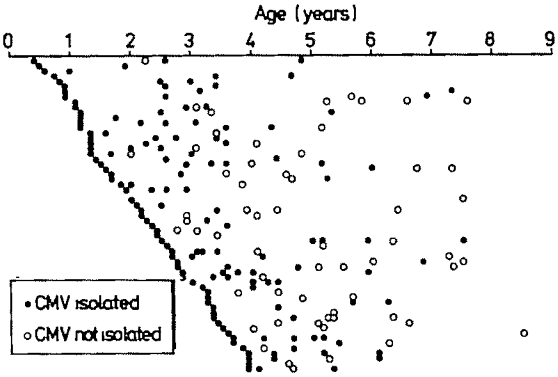

Figure *Testing of urine for cytomegalovirus in 60 children attending Nuffield Hearing and Speech Centre (1976–1980)*

The 60 children with CMV detected in their urine at the initial test comprised 39 with sensorineural deafness, 13 with speech problems but normal hearing, two with an acquired hearing loss, and six with a conductive hearing loss. The distribution of

Table 3 *Associated clinical problems in 60 children with CMV in the urine and 60 controls*

| | *Children with CMV in the urine (n=60)* | *Control children (n=60)* |
|---|---|---|
| Congenital sensorineural hearing loss alone | 31 | 37 |
| Congenital sensorineural hearing loss with | | |
| Mental retardation | 1 | 0 |
| Mental retardation, cerebral palsy, no speech | 1 | 0 |
| Mental retardation, unilateral blindness | 1 | 0 |
| Mental retardation, severe behaviour problems | 1 | 0 |
| Motor incoordination, severe hyperactivity | 2 | 0 |
| Bone dysplasia | 1 | 1 |
| Congenital rubella syndrome | 1 | 0 |
| Congenital dislocation of hips | 0 | 1 |
| Talipes | 0 | 1 |
| Absent nipples and lacrimal duct | 0 | 1 |
| Speech problem but normal hearing alone | 5 | 9 |
| Speech problem but normal hearing with | | |
| Epilepsy, clumsy | 1 | 0 |
| Facial palsy | 1 | 0 |
| Mental retardation, behaviour problem | 2 | 0 |
| Mental retardation, motor incoordination | 2 | 0 |
| Delayed development, motor incoordination, squint | 1 | 0 |
| Delayed development, clumsy | 1 | 0 |
| Motor incoordination | 0 | 1 |
| Talipes | 0 | 1 |
| Acquired sensorineural deafness | 2 | 2 |
| Conductive deafness | 6 | 6 |

diagnostic categories was similar for the 60 control children (table 3). Comparison between the group positive for CMV and the controls showed no differences in maternal pregnancy history, including pre-eclampsia, urinary tract infection, hypertension, hyperemesis, or mode of delivery. Rubella infection in pregnancy was, however more common in the control group of mothers (nine cases) than in the group positive for CMV (four cases). All 13 children whose mothers had a history of rubella in pregnancy had a sensorineural hearing loss.

The reported mean birth weight of 57 children positive for CMV was 3050 g and that of 54 controls 3260 g. There was no difference between the two groups in parents' reports of perinatal problems including jaundice, infections, breathing difficulties, or whether the infant had been nursed in an incubator.

There were two children, both shedding CMV, in whom congenital CMV hearing loss was a likely diagnosis. In one, CMV was reported to have been isolated during the neonatal period, but as the infant had been jaundiced and had received an exchange blood transfusion congenital CMV could not be distinguished from acquired CMV infection. The second child had symptoms compatible with congenital CMV (splenomegaly, petechiae, and jaundice) in the neonatal period but had also received a blood transfusion.

Table 3 shows the associated clinical problems in the 60 children with CMV in the urine and their controls Most of the children in both groups had no associated problems, but neurological abnormalities were recorded more often among those excreting CMV than among the controls.

## Discussion

The presence of CMV in the urine of a child with congenital sensorineural deafness does not imply that CMV is the cause of the hearing impairment. CMV is common in young infants. In one study 12% had acquired the infection by 3 months and 20% by 1 year; these children continued to shed CMV in their urine for years.[7] The diagnosis of congenital CMV infection can be made only if the virus is isolated in the first three weeks of life or if CMV IgM is found in a serum sample collected at or shortly after birth.[17] As routine screening for CMV at birth is not carried out and would not be practicable, the 90% of infants with congenital CMV infection who are asymptomatic at birth will not be diagnosed. Should they subsequently develop a hearing impairment its cause will remain unknown.

Our finding that CMV shedding was significantly higher among children with sensorineural deafness than among children with normal hearing empha sises the importance of CMV as a cause of hearin impairment. This was further supported by th higher prevalence of CMV in the urine of childre with hearing impairments who had no family histor of deafness than among those with a clear famil history, and by the higher prevalence of CMV in th urine of children with an uncertain history c congenital rubella compared with those in whom th diagnosis was more likely.

Apart from a history of maternal rubella, ther were no differences in the antenatal or perinata histories of children with and without CMV in th urine. This was not unexpected because congenita CMV is nearly always asymptomatic in both th mother and her infant. Examination of the clinica records showed that associated abnormalities suc as motor incoordination, mental retardation, an behaviour problems were more common among th children with CMV infection than among those fro whom virus was not isolated. It is not possible however, to draw conclusions from such sma numbers As destruction of the cochleolabyrint system, either selectively or completely, may occu after subclinical congenital CMV infection,[19] ves tibular abnormalities may be present in cases c focal CMV hearing loss or even in children wit normal hearing. Although no specific clinical pictur emerged, the finding that more of the children wit CMV infection had problems of motor coordinatio suggests that this may be so.

The more detailed analysis of the 60 children wit CMV in the urine at the initial examination show the persistence of viral shedding in children wit CMV infection. More surprising was the finding tha only one child from the group from whom no CM was isolated at the first examination subsequentl shed virus, and then only on one occasion. Thi suggests that despite regular contact with othe children, acquired infection was not common.

Some degree of hearing loss is the most commo irreversible sequela of congenital CMV infe tion.[4 5 8–12] The probability of sensorineural hearin loss in children with symptomatic congenital infectio is about 30%,[5] although even higher rates have bee reported.[4] This symptomatic group, however, rep resents fewer than 10% of congenitally infecte children. The more important issue is the prevalenc of sensorineural deafness in the remaining 90% wit asymptomatic congenital infection who, even with much lower risk of subsequent hearing loss, wi contribute substantially to the number of childre with hearing impairment born each year.

Prospective studies of children with diagnose asymptomatic congenital CMV report wide vari tions in the incidence of hearing impairment.[7 9 10 12

This variation in the reported risk of deafness is due to the inclusion of minor degrees of hearing loss, some of which is unilateral and temporary. When children with more severe degrees of deafness are included—for example, those who require special educational provision—the prevalence of hearing loss reported in each study remains fairly consistent. Of over 200 children with asymptomatic congenital infection enrolled in prospective studies, about 10% have this degree of hearing loss and in 6% it is bilateral.[13] There have been a few reports of progressive hearing loss in children with congenital CMV,[4 21] but the likelihood of progression from mild to functionally important hearing loss seems to be small, although this is consistent with the results of histological examination in the few cases already mentioned.[15]

Because of the reduction in hearing loss due to congenital rubella infection following the introduction of immunisation against rubella the role of CMV as a cause of deafness has become increasingly important.

Assuming that there are 600 000 births each year in England and Wales and, that the rate of congenital infection with CMV is three in every 1000 births, 1800 children will be born with congenital CMV infection each year. If 6% of these children have a severe, bilateral, sensorineural hearing loss as estimated from prospective studies, this would amount to 108 congenitally infected children each year. Assuming that the incidence of moderate to severe bilateral deafness is one or two in every 1000 live births[22 23] congenital CMV could account for 108 (12%) of the 900 children with sensorineural deafness born annually.

We are grateful to the following organisations for financial support the Wellcome Trust; the National Fund for Crippling Disease, and the Board of Governors, the Hospital for Sick Children, Great Ormond Street We also thank the department of Microbiology, and Sister Ahkhan at the Nuffield Speech and Hearing Centre who collected all the specimens

When this investigation started Dr WC Marshall was senior lecturer at the Institute of Child Health under the Wellcome Trust's University Award scheme studying the effect of intrauterine infection on the fetus and the infant in the short and long-term Bill Marshall brought all his energy, enthusiasm, and experience to this particular study, which sadly he did not live to see completed

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# Postnatal sensitivity of the peripheral chemoreceptors in newborn infants

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SUMMARY The peripheral chemoreflex was tested in healthy term infants by measuring the ventilatory response to 100% oxygen over 30 seconds. Minute ventilation did not change when studied two to six hours after birth. By contrast, at 2–6 days of age a mean decrease of 9·8% was noted, the difference between the groups being highly significant. There were no significant changes in respiratory rate. It is concluded that the chemoreflex is less active immediately after birth than it is a few days later, possibly due to a resetting of the sensitivity of the peripheral chemoreceptors from the fetal state, with its relatively low arterial oxygen tension to the higher postnatal concentrations.

Carotid chemoreceptors have been reported to be silent in fetal sheep and it has been assumed that they are activated at or shortly after birth by the sympathetic nervous system.[1] Studies in human neonates have shown active chemoreflexes both in term and preterm infants.[2 3] Girard *et al,* on the other hand, found no effect on ventilation when they produced 'physiological chemodenervation' with 100% oxygen in infants 1–19 hours of age, and speculated that peripheral chemoreceptors were not activated until some time after birth.[4]

The concept that the carotid chemoreceptors do not respond before birth has recently been challenged by Blanco *et al,*[5] who found that peripheral chemoreceptors in fetal sheep were active and responsive.[5] They could not, however, show any spontaneous chemoreceptor activity in newborn lambs until a few days after birth. Their interpretation was that the 'set point' of the sensitivity of the peripheral chemoreceptors changed from the low oxygen tension in the fetus to the adult range during the first few days of life.

These contradictory findings prompted us to reinvestigate peripheral chemoreceptor activity in newborn infants.

## Subjects and methods

Sixteen newborn infants born at term (12 boys and four girls) were studied. They were all delivered vaginally after uncomplicated pregnancies. In the group of the 11 mothers whose infants were studied on the day of birth six received pudendal nerve blocks and six were given pethidine during labour; four received both types of analgesia. There were no signs of asphyxia, all Apgar scores being 7 or more at one minute. Mean birth weight was 3815 g, ranging 2910–4530. All infants were healthy on examination before the test. The parents were approached in the delivery room and informed consent was obtained. The study was approved by the local ethical committee.

To determine the influence of the peripheral chemoreceptors on normal breathing in air, we assessed exhaled volumes before and after administration of pure oxygen. Volume measurements were made with a Greer Electrospirometer CS5 (Mercury Electronics, Scotland), the flowhead being connected by a short tube to an infant face mask (Bennett Medical Equipment, Los Angeles, California, USA). The flowhead was connected distally via a T tube to a warmed humidified stream of air set at five l/minute, which could be rapidly changed to pure humidified oxygen.

Expiratory flow was integrated electronically to obtain tidal volumes. The total dead space of the system was estimated to be 7 ml. We had no access to a capnograph at the time of the present study, so we assessed the build up of carbon dioxide in the mask in a separate experiment using the same equipment. Inspired carbon dioxide was measured with a capnograph during steady state conditions and was less than 1%. The system was calibrated with 10, 15, and 20 ml of humidified air and oxygen.

Volume readings were about 10% higher with pure oxygen than with air due to the difference in the viscosity of the gases. Because exhaled rather than inhaled volumes were measured and the oxygen concentrations of the individual breaths change during the breathing cycle, no corrections to allow for this difference were made In some cases inspired oxygen concentrations were estimated indirectly using a nitrogen analyser (505 Nitralyzer, MedScience, Needham Heights, Massachusetts, USA) and taking samples from the tubing between the mask and the flowhead. Tidal flow, tidal volumes, and nitrogen concentrations were recorded on a chart recorder (Mingograph, Elema-Schönander, Sweden).

The test was performed during quiet sleep two to six hours after birth and at 2–6 days of age. Quiet sleep was assessed by behavioural criteria, including regular breathing apart from sighs and the absence of eye movements and gross body movements apart from startles

The mask was gently applied to the infant's face and then firmly held; most babies tolerated this well In some cases they became restless but soon returned to quiet sleep. After the readings had become stable, recordings were made for at least 30 seconds before air was substituted for the oxygen for the same length of time. In those cases where the test was repeated in the same session at least three minutes elapsed between the runs.

Tidal volumes and respiratory rate were calculated during a 30 second control period and 30 seconds of oxygen administration. Percentage changes in exhaled volumes and changes in breathing frequencies were determined using each infant as his or her own control. Differences in respiratory rate and percentage changes in ventilation were analysed by Student's *t* test for independent samples, regarding each test as an independent event. All values are expressed as mean (SD).

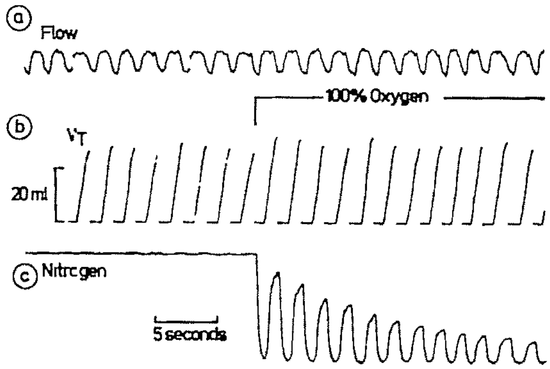

Fig 1 *Tracing from hyperoxic test in a 6 hour old infant. From top to bottom: flow, integrated tidal volumes ($V_T$), and expired nitrogen.*

## Results

The test performed two to six hours after birth comprised 13 trials in 11 infants. At 2–6 days of age we carried out 12 tests in eight babies. Sequential recordings—that is, acceptable tests both on the day of birth and a few days later—were obtained in three infants. A representative recording is shown in fig 1.

During the control period ventilation was 211 (80) ml/kg/minute in the younger group and 218 (56) ml/kg/minute among the older babies. There was no correlation between ventilation during the control period and the response to hyperoxia. Results were reproducible in half the infants when the test was

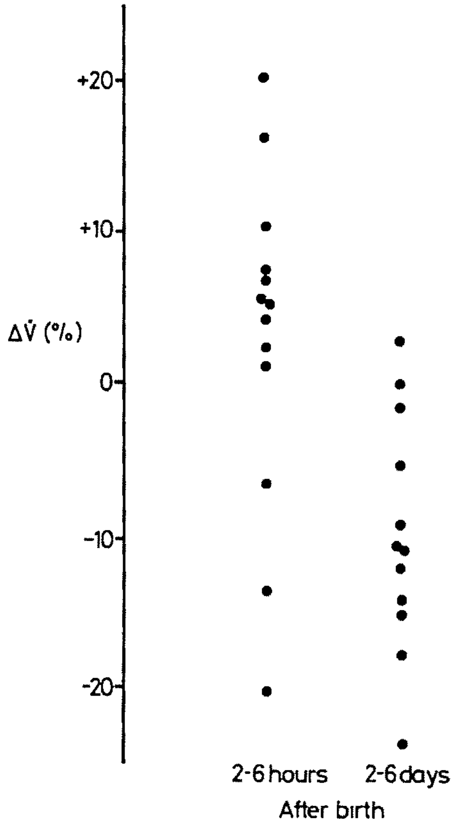

Fig 2 *Percentage change in exhaled volumes ($\Delta V\%$) on exposure to 100% oxygen for infants 2–6 hours after birth (left) and at 2–6 days of age (right)*

repeated at the same age The most the results differed between tests was 13·6%.

The percentage change in ventilation when the infants were made hyperoxic is shown in fig 2. There was an insignificant mean increase of 3·1 (11·1)% in the youngest group. In contrast, the older infants decreased their minute ventilation by 9·8 (7 7)% ($p<0·01$). The difference in ventilatory response between the two age groups was significant ($p<0·01$) Among the infants 2–6 hours old respiratory rate changed from 40·0 (12 0)/minute to 38·8 (10 3)/minute. In the infants 2–6 days old the mean frequency decreased from 38·4 (8·9)/minute to 36·6 (6 8)/minute. The changes in respiratory rate were not significant. The reduction in ventilation was therefore mainly due to a decrease in tidal volume.

## Discussion

Prolonged exposure to hyperoxia causes an initial decrease in ventilation followed by a sustained increase. The primary response is ascribed to the peripheral chemoreceptors, the late increase may be due to several factors—for example, changes in cerebral blood flow and arterial carbon dioxide tension ($PCO_2$).[6]

The '$O_2$ test' was proposed by Dejours[7] to estimate the influence of the peripheral chemoreceptors on ventilation. A short term stimulus affects the arterial chemoreceptors rapidly, and the effect may be recorded before any secondary influences are apparent. The method was first used in newborn infants by Girard *et al* to evaluate the postnatal activity of the peripheral chemoreflex.[4] Purves[5] criticised the test pointing out that a single breath of oxygen may not raise arterial oxygen tension ($PO_2$) sufficiently because of the high degree of venous admixture in arterial blood caused by shunts in the newborn To circumvent this problem we used a somewhat longer oxygen exposure. We believe that 30 seconds is long enough to raise arterial $PO_2$ to sufficient hyperoxic concentrations without being affected by the normal fluctuations in breathing volumes. The time should still be short enough to avoid central chemoreceptor stimulation due to consequent increases in $PCO_2$.

A feature of this study was the strict age grouping in the immediate postnatal period. The finding that hyperoxia decreases ventilation in infants 2–6 days old while minute ventilation is less affected two to six hours after birth suggests an increasing influence of the hypoxic ventilatory drive during the first days of life Our results are consistent with the finding of a resetting of the sensitivity of the peripheral chemoreceptors after birth in newborn lambs.[5] Jansen *et al* showed that the peripheral chemoreceptors are not essential for intrauterine breathing movements or for the establishment of effective breathing at birth.[9]

Our figures for the decrease in ventilation when the older infants were made hyperoxic are somewhat lower than those presented by others This may be explained by the fact that we integrated the expired flows. Pure humidified oxygen gave about 10% higher readings than air on the pneumotachograph We did not correct for this because the composition of the expired gas changes breath by breath. Because the differences between the groups were based on percentage changes in ventilation before and after hyperoxia, such a correction would most likely not have influenced the results.

There may be some doubt about assessing the relative contribution of the hypoxic drive to the central controller of ventilation from the ventilatory output, which may in turn be affected by several other factors. These include auditory, tactile, and thermal stimuli as well as the analgesics given to the mother during labour, and they are probably not of constant and equal importance in all babies. This may in part explain the variation in responses, both between different runs in the same infant and between different infants. Thus the test results of individual babies are difficult to interpret The influence of a possible build up of carbon dioxide in the mask cannot be excluded. No correlation was found, however, between ventilation during the control period and the hyperoxic response. We found no obvious explanation for the finding that some of the older infants did not decrease ventilation when made hyperoxic. There may be variation between babies in the time needed for the postnatal adaptation. The overall picture is, however, clear. there is a difference in response between the age groups, and the three infants tested at different postnatal ages all showed an increased response over the first days of life.

Several investigators have found an active chemoreflex in newborn infants, although the age of their subjects has not been confined to the first days of life. Cross and Warner reported a decrease in ventilation in response to oxygen even during the first days of life.[2] Interestingly, their babies studied on more than one occasion showed more pronounced decreases as they grew older, a finding which is not commented on by the authors but is in agreement with our results. Girard *et al* found that a single breath of 100% oxygen failed to affect ventilation in infants 1–19 hours old while older babies responded with a decrease in ventilation [4]

The postnatal arterial oxygen tension seems to influence the degree of sensitivity. People born at high altitude in the Andes have a weaker hypoxic response than those born at sea level This lower sensitivity seems to be irreversible, as those born at high altitude moving to sea level and lowlanders moving to high altitude exhibit the same responses as controls remaining at high altitude and sea level, respectively.[10 11] The same authors suggested that infants with chronic hypoxia and cyanotic heart failure from birth acquire a permanent low chemoreceptor sensitivity.[12] This has been disputed by Edelman *et al,* however, who, using a different method, reported that patients with tetralogy of Fallot restore their sensitivity to hypoxia after corrective surgery.[13]

The present findings suggest, in agreement with Blanco *et al*, that the sensitivity of the peripheral chemoreceptors noticeably changes during the first days after birth.[5] Postnatal oxygen tension seems to determine the sensitivity threshold but other perinatal factors may play a part—for example, drugs given to the mother and catecholamine concentrations in the newborn. The clinical implications may be, as pointed out by Hanson,[14] that an asphyxiated infant develops a delayed resetting of the oxygen sensitivity due to prolonged hypoxemia and an increased susceptibility to hypoxemia due to low sensitivity of the peripheral chemoreceptors; this in turn leads to a further delayed resetting. This concept emphasises the importance of adequate postnatal $PO_2$ concentrations to ensure an optimal adaptation to extrauterine life

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# Effects of theophylline on ventilatory response to hypoxic challenge

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SUMMARY The respiratory and arousal responses to mild hypoxia during quiet sleep were studied using inductive plethysmography and transcutaneous gas electrodes in 11 apnoeic infants before and after the administration of oral theophylline (3 mg/kg). Theophylline changed the ventilatory response to a more biphasic pattern—that is, ventilation decreased after an initial increase. The relative ventilatory slope (defined as the decrease in transcutaneous carbon dioxide tension ($PCO_2$) in relation to the fall in transcutaneous oxygen tension ($PO_2$)) decreased significantly after theophylline. Four infants were roused during hypoxia before theophylline administration compared with none after treatment. Theophylline abolished the periodic breathing induced by hypoxia in one of six infants. These findings suggest that methylxanthines may not, as previously thought, enhance the respiratory drive during hypoxia.

Methylxanthine derivatives are widely used as respiratory stimulants both in low birthweight infants with idiopathic apnoea and in those with apnoea of infancy. These compounds increase the respiratory drive and reduce the number of apnoeic episodes both in premature[1 2] and older apnoeic infants.[3 4] Theophylline has also been assumed to increase the ventilatory and arousal responsiveness to hypoxia in babies with apnoea of infancy.[3] Experimental studies in newborn animals, however, have shown contradictory results.[5 6] In man investigations have so far only been performed in adults.[7 8]

The aim of this study was to investigate whether theophylline given before a hypoxic challenge increased the ventilatory and arousal responsiveness. Two hypoxic challenges, one before and one after the administration of theophylline, were performed during the same night in 11 infants with severe apnoeic events associated with sleep.

## Patients and methods

The study was approved by the local ethical committee and informed parental consent was obtained in all cases. Seven boys and four girls who had had a potentially life threatening apnoeic episode were entered in the study. Their median age at the time of the recording was 10 weeks (range 3–21). These 11 infants were part of a larger group of apnoeic infants recently evaluated in a prospective collaborative study.[9]

The respiratory investigations comprised a 10 minute hypoxic challenge with 15% oxygen in nitrogen. A warmed and humidified hypoxic gas mixture was delivered at a rate of 6–8 l/minute through a 10 l plastic hood covering the head and neck. The tests were performed in standardised conditions (the environmental temperature was 24°C, and the lights were dimmed) during quiet sleep.[10] The control test was carried out between 9 and 11 pm. The infants were lying prone and after a five minute stable control period in air the hypoxic gas mixture was delivered for 10 minutes. The test was repeated between 0 and 2 am, about one hour after administration of an oral dose of theophylline cholinate 3 mg/kg.

Recordings during uninterrupted natural sleep were a matter of prime concern in the investigation; to avoid the disturbance of blood sampling plasma theophylline concentrations were not determined.

The ventilatory response to hypoxia was assessed by inductance plethysmography (Respitrace, Ambulatory monitoring, Ardsley, New Jersey, USA). Minute ventilation was defined as the sum of the rib cage and abdominal movements during each minute of the test. The inductance plethysmography device was calibrated in arbitrary units and ventilation was expressed as the percentage change from the control period.

In addition, an index of ventilatory responsiveness to hypoxia in relation to the prevailing metabolic needs was calculated from the trancutaneous gas changes. This index, 'relative ventilatory slope', is defined below; a more extensive justification for this approach has been given elsewhere.[11]

Transcutaneous electrodes (Radiometer TCM1 and TCM2, Copenhagen, Denmark) were used to estimate arterial gas pressures. The probes were positioned on the abdomen at the costal margin. A 45°C temperature setting was used for the transcutaneous oxygen ($tcPO_2$) and 43°C for the transcutaneous carbon dioxide ($tcPCO_2$) electrode. The $tcPO_2$ electrode was calibrated to ambient barometric pressure and the $tcPCO_2$ electrode to two carbon dioxide mixtures of known concentration.

The principles of the data analysis are illustrated in a representative recording from one patient (fig 1). $TcPO_2$ values were taken from the original tracing every 15 seconds and paired with the $tcPCO_2$ values obtained 60 seconds later (fig 1, top). This correction was made to compensate for the delay of the $tcPCO_2$ electrode.

The relative ventilatory slope was defined as the change in $tcPCO_2$ in relation to the fall in $tcPO_2$. Each deflection from the control value of $tcPCO_2$ ($\Delta tcPCO_2$) was plotted against the corresponding inverted $tcPO_2$ value and a regression line was fitted, using the method of least squares (fig 1, middle).

A negative relative ventilatory slope suggested a relative increase in ventilation, because $tcPCO_2$ decreased in response to the hypoxic challenge. Correspondingly, a positive slope was taken as showing a relative decrease in ventilation because $tcPCO_2$ increased in response to the hypoxic provocation. The mean rate of decrease in $tcPO_2$ was also calculated by regression analysis. The curvilinear decay of the $tcPO_2$ is shown by plotting the $tcPO_2$ values on a semilogarithmic scale (fig 1,

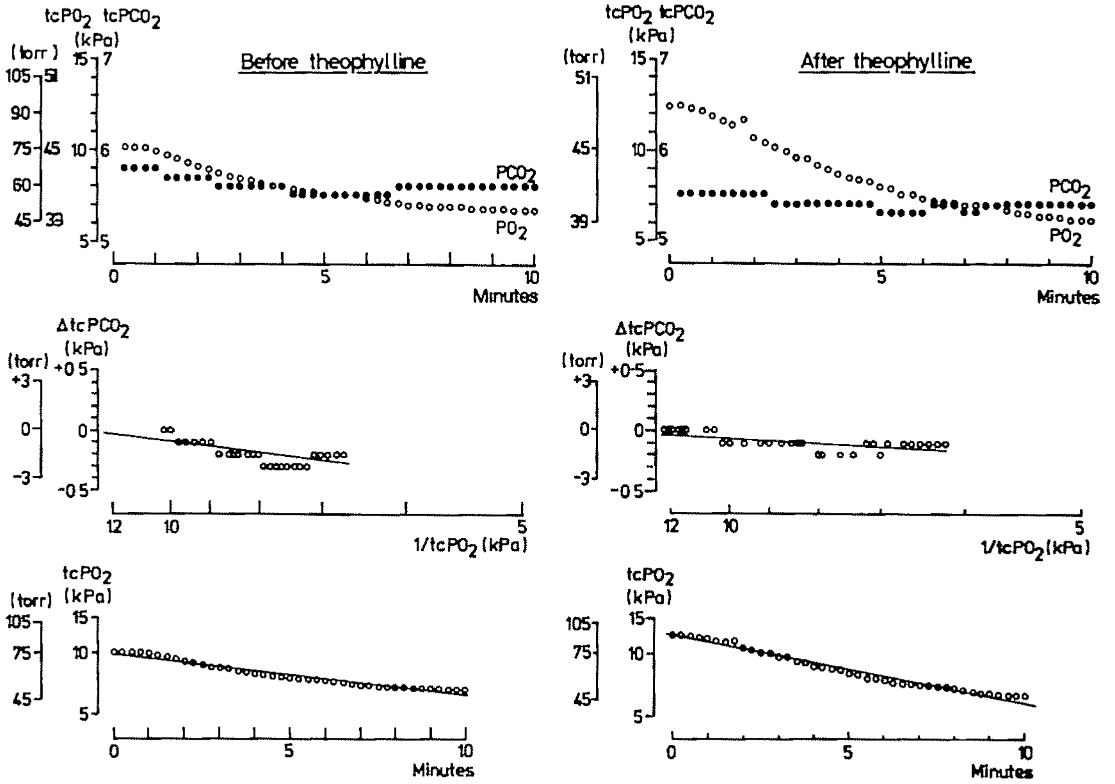

Fig 1 *Transcutaneous oxygen and carbon dioxide measurements recorded during one hypoxic episode in a 6 week old girl with apnoea of infancy.* Top—*$tcPO_2$ and $tcPCO_2$ sampled every 15 seconds during 10 minute test.* Middle—*Regression line representing relative ventilatory slope Each deflection from control $tcPCO_2$ ($\Delta$ $tcPCO_2$) is plotted against corresponding inverted $tcPO_2$ value Negative slope indicates relative increase in ventilation.* Bottom—*Regression line representing rate of $tcPO_2$ decrease. $TcPO_2$ curve of bottom panel is plotted on a semilogarithmic scale.*

bottom). The main purpose of this analysis was to relate the occurrence of hypoxic arousal to the rate of fall in $PO_2$

Periodic breathing was defined as three or more regularly recurring episodes of respiratory arrests of more than 3 seconds in duration interrupted by periods of regular breathing of less than 20 seconds. Arousal was defined as crying and opening of the eyes or signs of discomfort and gross body movements for at least 20 seconds. The $tcPO_2$ and $tcPCO_2$ values of the last minute prior to the test were used as baseline measurements.

The respiratory data of each baby before and after the administration of theophylline were compared by Student's *t* test, repeated measures design. Fisher's exact test was used to assess the significance of differences in incidence of arousal and periodic breathing before and after treatment. Regression analysis was used to determine slopes and relations.

## Results

Most infants increased their ventilation about 20% over the control period in response to the hypoxic provocation and sustained this increase throughout the 10 minutes of hypoxia (fig 2). After administration of theophylline a similar increase in ventilation was observed. The rise in ventilation, however, was not sustained to the same extent as before treatment (fig 2) Although the ventilatory response to hypoxia varied considerably among individual babies, the altered response pattern after theophylline administration was a consistent observation.

The effect of theophylline on $tcPO_2$ and $tcPCO_2$ measurements in a six week old girl is shown in fig 1; her response pattern was representative of the whole group of infants After theophylline administration there was a significant increase in mean (SD) baseline $tcPO_2$ tension (1·8 (1·6) kPa; $p<0\cdot005$) and a significant decrease in mean (SD) baseline $tcPCO_2$ tension (0·5 (0·4) kPa; $p<0\cdot0009$). The relative ventilatory slope (non-dimensional index) decreased on average 1·6 (1·5) ($p<0\cdot02$) after theophylline, indicating a relative decrease in ventilation.

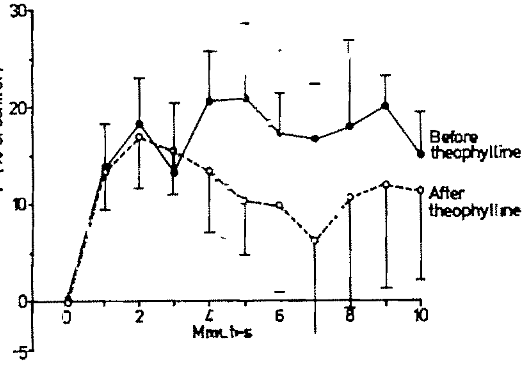

Fig 2 *Minute ventilation during hypoxia assessed by inductive plethysmography. Mean (SD) ventilatory response=% of control; matched data only included.*

The mean rate of decrease of $tcPO_2$ during the hypoxic challenge was not significantly affected by theophylline. The average decrease (here expressed in logarithmic units as $-\log_e$ kPa/minute) was $-0\cdot059$ (0·028) before and $-0\cdot064$ (0·028) after treatment. The mean lowest $tcPO_2$ tension remained unchanged, being 5·2 (1·4) kPa before and 5·5 (1·5) kPa after theophylline administration.

All infants breathed regularly during the control period. Theophylline abolished periodic breathing induced by hypoxia in only one of the six infants who had this breathing pattern before treatment. Four infants were roused before theophylline administration compared with none after treatment.

## Discussion

The two main findings of this study are that theophylline does not increase ventilatory responsiveness to hypoxia, and it has no consistent effects on the periodic breathing induced by hypoxia. Furthermore, arousal responsiveness seemed to decrease after treatment with theophylline. These effects of theophylline during hypoxia contrast strongly with its well known stimulatory effects on respiration during air breathing.

After theophylline administration baseline $tcPO_2$ tension increased and baseline $tcPCO_2$ tension decreased significantly. This suggests an increase in resting ventilation, which confirms previous observations[1] Because $tcPO_2$ tensions were higher and those of $tcPCO_2$ lower after theophylline administration, a less pronouced immediate ventilatory response to hypoxia could be expected due to the lower chemoreceptor stimulation, both peripherally and centrally. This was not found, as the degree of the initial ventilatory response was not affected by theophylline. The immediate response to hypoxia is largely mediated by carotid body chemoreceptor activity, and therefore the unchanged responsiveness (in spite of higher baseline $tcPO_2$ tensions) may suggest that theophylline has some stimulatory effects on peripheral chemoreceptors.[12]

The hypoxic respiratory responsiveness was estimated by analysing the changes in $tcPCO_2$ in relation to the fall in $tcPO_2$. Measurements of pulmonary ventilation alone may not be adequate to interpret the hypoxic ventilatory response in infants because any observed changes in ventilation may also be secondary to changes in metabolic rate. This was particularly true in the present investigation because theophylline increases oxygen consumption even in the low dose used.[1]

The main purpose of analysing the transcutaneous gas changes was to distinguish between a real ventilatory depression—that is, a decrease in ventilation accompanied by a rise in $PCO_2$—and a —decrease in ventilation with no increase in $PCO_2$ that is, a decrease probably appropriate for the prevailing metabolic demands. Another aim was to relate the response to actual $PO_2$ concentrations as the same fraction of inspired oxygen may produce different degrees of hypoxia in two different tests due to differences in resting concentrations of $PO_2$ and body oxygen stores.

The initial increase in ventilation was not sustained to the same extent after theophylline. This late fall seemed to reflect a real decrease in alveolar ventilation because the index of $tcPCO_2$ decrease in relation to the fall in $tcPO_2$ diminished significantly.

Similar effects of theophylline on the response characteristics—that is, unchanged initial ventilatory response followed by a decrease—have previously been seen in a more extensive investigation of piglets paralysed and servoventilated after vagotomy.[6] The increase in ventilatory drive during hypoxia (measured as phrenic discharge) was less sustained after theophylline administration.

The mechanisms producing this late fall in ventilation are obscure, and there may be several explanations. Adenosine is released in the brain during hypoxia[13] where it depresses ventilation by a central mechanism,[14] and increases breathing via peripheral chemoreceptors.[15] Many of the respiratory effects of theophylline are mediated by its antagonistic effects on adenosine.[16] Adenosine is released in the brain at a lower $PO_2$ than in peripheral tissues [17] During this relatively mild hypoxia theophylline may have interfered mainly with the peripheral actions of adenosine, that is, its stimulatory effects on carotid chemoreceptors.

An alternative explanation is that theophylline (by decreasing cerebral blood flow velocity [18] and by lowering arterial $PCO_2$) may make the brain hypoxaemic leading to a decrease in ventilation [19] This mechanism could also explain the lower rate of arousal seen after treatment. A decrease in cerebral blood flow interferes with the ability to become aroused [20]

The original observation by Vogl that methylxanthines abolish periodic breathing when breathing air has been repeatedly confirmed in both infants and adults.[21] In his study no clear-cut effects on periodic breathing induced by hypoxia were observed. Cherniack *et al* have shown that in adult cats an increased hypoxic drive (a decrease in $PO_2$) in conjunction with a decreased carbon dioxide drive (a decrease in $PCO_2$) can elicit regular periodic breathing.[22] Theophylline has been reported to shift the carbon dioxide response curve to the left.[1] This change in carbon dioxide threshold may counteract the stabilising effects of theophylline on respiratory control.

In healthy adults aminophylline has been reported to increase hypoxic ventilatory responsiveness, but only when alveolar $PCO_2$ was raised to pretreatment concentrations.[7] [8] It was therefore concluded that methylxanthines increase hypoxic responsiveness, although this effect was masked by the relative hypocapnoea produced by these compounds. Raising the $PCO_2$ to concentrations prevailing before theophylline administration, however, will stimulate breathing both by peripheral and central mechanisms.[23] This complex interaction may not allow definite conclusions to be drawn on the responsiveness to hypoxia.

The results of this study do not contradict the view that methylxanthines may diminish the risk of sleep related apnoeic episodes by increasing baseline oxygen concentrations. They do, however, suggest that the concept of increasing hypoxic responsiveness by treatment with theophylline is questionable. To determine whether the observed decrease in the ventilatory and arousal response is of clinical importance needs further evaluation. Nevertheless, it is suggested that methylxanthines should be used with some caution in babies with apnoea of infancy.

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# Cerebral blood flow velocity variability in infants receiving assisted ventilation

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SUMMARY Cerebral blood flow velocity was measured using Doppler ultrasonography in 20 babies who weighed less than 2500 g at birth and who were receiving assisted ventilation; their patterns of spontaneous respiration were recorded simultaneously. The babies were induced to breathe synchronously or asynchronously with the ventilator by manipulating the inspiratory and expiratory time settings. The variability of cerebral blood flow velocity (coefficient of variation) was calculated from the area of the maximum Doppler frequency shift envelope for 10 cardiac cycles from 211 recordings made on 42 occasions, and was greatest within 12 hours of birth after which it fell progressively over the next 48 hours.

Variability of cerebral blood flow velocity was significantly greater when the infants were breathing out of synchrony with the ventilator (median 11%, interquartile range 8–14%) than when they were either apnoeic (median 5%, 3–7%), or breathing synchronously with the ventilator (median 5%, 3–6%).

Perlman *et al*[1] reported a large variability from beat to beat in the blood flow velocity in the cerebral arteries of some premature neonates using continuous wave Doppler ultrasonography. Twenty one of the 23 infants with wide variability developed intraventricular haemorrhages and possibly the transmission of fluctuations from the systemic arterial blood pressure to the capillaries of the germinal matrix led to their rupture. A pronounced reduction in the incidence of intraventricular haemorrhage was achieved by selective paralysis of infants with wide variability in blood flow velocity, with pancuronium.[2] The authors suggested that the infants' respirations that occurred out of synchrony with the ventilator were responsible for this variability, and elimination of spontaneous respiration by pancuronium caused the reduction in the incidence of haemorrhage. Unfortunately no recordings of respiration were made to confirm this hypothesis. Pancuronium may have had its effect either by reducing non-respiratory movements or by some direct action on the circulation.

Selective paralysis with pancuronium of high risk infants may reduce the risk of intraventricular haemorrhage, but unfortunately the drug may have cardiovascular side effects[3] and may necessitate the use of higher ventilator pressures to maintain adequate oxygenation.[4] Alternative measures for infants who breathe against the ventilator are triggered ventilators[5] or the induction of synchronous ventilation by manipulation of ventilator timing.[6] Selective paralysis of infants who breathe out against ventilator inflations[7] or who require defined peak pressures and rates[8] has reduced the incidence of pneumothoraces but this has not been associated with a noticeable reduction in the incidence of intra ventricular haemorrhage.

One hypothesis to explain the fluctuations in the velocity of cerebral blood flow is that swings in intrathoracic pressure, resulting from the combination of artificial and spontaneous respiration, change cardiac stroke volume and venous return to the heart. These then change arterial and venous pressures, which in turn affect cerebral blood flow.

This study aimed to examine the variability in cerebral blood flow velocity over the first 72 hours of life, particularly in relation to the pattern of interaction between spontaneous respiration and artificial ventilation.

## Patients and methods

Infants, weighing less than 2500 g at birth who were admitted on the first day of life to the neonatal intensive care unit and receiving artificial ventilation were considered for the study. Infants who had an intraventricular haemorrhage detected by ultrasound scan at the time of the first study, or who had a major congenital malformation were excluded, as was any infant admitted when one of the investigators was not available. Each infant was studied up to four times: at less than 12 hours of age and within six hours of 24, 48, and 72 hours of age. No further studies were made if the infant was paralysed, taken off the ventilator, or had sustained an intraventricular haemorrhage. During each study simultaneous recordings of blood flow velocity and respiratory interaction patterns were made by independent observers.

The variability of cerebral blood flow velocity was measured using a Duplex ultrasound scanner with range gated Doppler sampling (Advanced Technology Laboratories Mk 600). The Doppler sample volume was positioned near the anterior or middle cerebral artery using the real time image, and fine adjustments were made to give the loudest possible signal. To reduce bias the timing of recordings of blood flow velocity was chosen by the observer of the respiratory patterns who was unaware of the Doppler tracings. Each recording of blood flow velocity lasted seven seconds and comprised a paper printout of the fast Fourier transform of the Doppler frequency shift. The recordings were coded and analysed at a later date. The area within the peak frequency envelope for the whole (systole and diastole) of each of 10 cardiac cycles was measured by computer assisted planimetry (graphics tablet connected to a microcomputer). This measurement was made twice and the mean of the two measurements used. The mean error of area measurement (difference/mean×100) was 5·2%. The variability of blood flow velocity was calculated as the coefficient of variation of spectrum area for the 10 cardiac cycles in each record (CV=standard deviation/mean, expressed as a percentage).

The baby's spontaneous respiration was monitored using a pneumatic respiration monitor (Graseby Dynamics MR10) taped just below the xiphisternum, as previously described.[9] The ventilator circuit pressure was measured using a transducer (Mercury Electronics) connected near the top of the endotracheal tube. Signals were recorded on a polygraph (Gould 2500 series) at 25 mm/second.

The patterns of spontaneous respiration observed during ventilation were classified as apnoea, synchrony, or asynchrony. Apnoea indicated that the baby showed no spontaneous respiratory activity during the recording, synchrony that the baby's inspiratory efforts were consistently in phase with the ventilator inflations, and asynchrony that the baby was breathing but with no regular association with the ventilator timing.

Six recordings were made on each occasion in one of two sequences: synchrony-asynchrony-synchrony or asynchrony-synchrony-asynchrony, two recordings being made during each phase. The sequence was chosen according to the pattern of interaction between the baby's respiration and the ventilator cycles observed at the start of each period. The sequences were used to eliminate any time or order effects. If the baby was apnoeic only two recordings were made. Each phase lasted 5 to 10 minutes and the whole study period was less than 30 minutes.

Babies were induced to breathe asynchronously by using a ventilator rate of 30/minute with an inflation time of 0·5 seconds and deflation time of 1·5 seconds. They were induced to breathe synchronously by using ventilator settings chosen to match their spontaneous inspiratory and expiratory timing.[6] The initial time settings for this were: rate 86/minute, inflation time 0·3 seconds, and deflation time 0·4 seconds. This was the average respiratory timing of a large comparable group of premature babies receiving ventilation who continued to breathe spontaneously.[10] If necessary the time settings were altered to produce the best possible synchrony between baby and ventilator. At the end of each study, the infants were left breathing synchronously when possible. Details of blood gas measurements and ventilator settings were recorded.

Associations between variables were examined using Spearman's test of non-parametric correlation. Comparisons between groups were made using the Mann-Whitney U test. The study was approved by the hospital ethical committee.

## Results

Twenty infants with a mean birth weight of 1336 g and a mean gestational age of 29·2 weeks were studied on 42 separate occasions. Between one and four studies were made on each baby, less than four studies being made in some babies because of neonatal death (n=2), intraventricular haemorrhage (n=1), or stopping of mechanical ventilation (n=15). The table shows the general information about the babies at the time of the studies.

Table *General information about 20 babies studied*

| *Measurement* | *Median* | *Range* |
|---|---|---|
| Gestation (weeks) | 29 | 26–39 |
| Birth weight (g) | 1336 | 630–1876 |
| Inspired oxygen (%) | 50 | 25–90 |
| Peak pressure (kPa) | 1·96 | 1·27–2·94 |
| $pO_2$ (kPa) | 8·5 | 5–19 |
| $pCO_2$ (kPa) | 5·0 | 3–8 |
| pH | 7·36 | 7·2–7·5 |

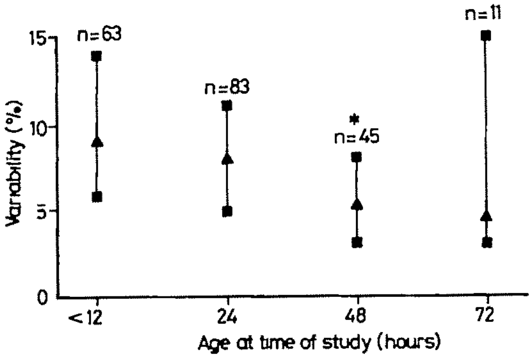

Fig 1 *Median variability in cerebral blood flow velocity and interquartile ranges for each study age.*
**=$p<0\cdot0001$ [v. less than 12 hours]*

Fig 1 shows, the overall variability of cerebral blood flow velocity for each of the postnatal study ages. Variability was greatest under 12 hours of age and this fell over the subsequent 36 hours. The variability was significantly lower at 48 hours of life than in the first 12 hours (Mann-Whitney U test, $p<0\cdot0001$). There was no further fall between 48 and 72 hours. The number of recordings made at 72 hours, however, was low and the range of variability wide. There were no significant differences in arterial blood gas measurements or ventilatory support between the recordings made at <12 hours old and 48 hours old that might have been responsible for the observed difference in velocity variability.

On five occasions the baby being studied was apnoeic Eighteen babies were studied in the sequence synchrony-asynchrony-synchrony and 17 in the alternate sequence. Apart from one baby who could not be induced to breathe synchronously on two occasions, synchronous ventilation was achieved within two minutes. In total there were nine recordings of apnoea, 102 of synchrony, and 100 of asynchrony. Figs 2 and 3 show examples of recordings made in one baby during periods of asynchrony and synchrony The medians and interquartile ranges of CV for each pattern of interaction were apnoea 5% (3 to 7%), synchrony 5% (3–6%), and asynchrony 11% (8–14%) (fig 4). The differences between asynchronous ventilation and each of the other two patterns were significant ($p<0\cdot0001$). There were no differences in heart rate variability from beat to beat among the three patterns of interaction. The CV was 7% for all groups. The difference between synchrony and asynchrony was significant at all postnatal study ages except 72 hours, when the number of recordings was too small for analysis (fig 5).

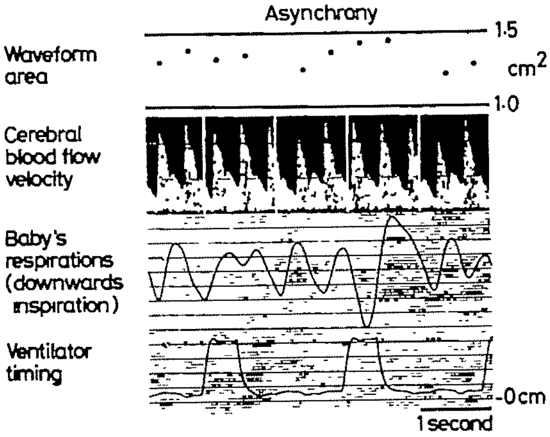

Fig 2 *Example of blood flow velocity and respiratory recordings for a baby during asynchronous breathing There is no regular correspondence between spontaneous respiratory pattern and ventilator. Note variability in waveform area*

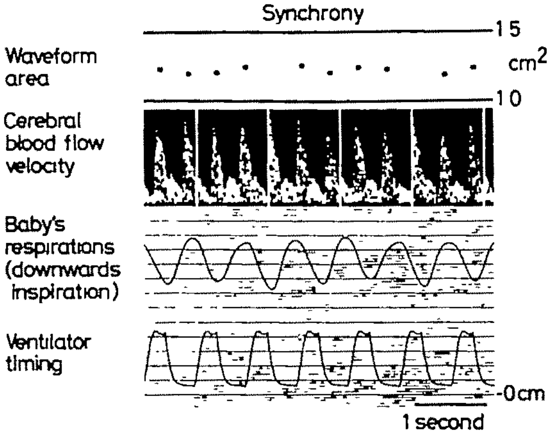

Fig 3 *Example of blood flow velocity and respiratory recordings for a baby during synchronous breathing. Note reduced variability in waveform area.*

No association was found between blood flow velocity variability and birth weight, gestational age, peak ventilator pressure, arterial oxygen or carbon dioxide tensions. There was a weak but significant association with pH, increasing pH correlating with increasing variability ($r_s=0\cdot23$, $p=0\cdot001$).

Of the 20 infants in the study three developed an intra ventricular haemorrhage. The predominant pattern of interaction at the onset of each study period was split equally between synchrony and asynchrony in these patients. There were no characteristic features to the waveform pattern of cerebral blood flow velocity in these babies.

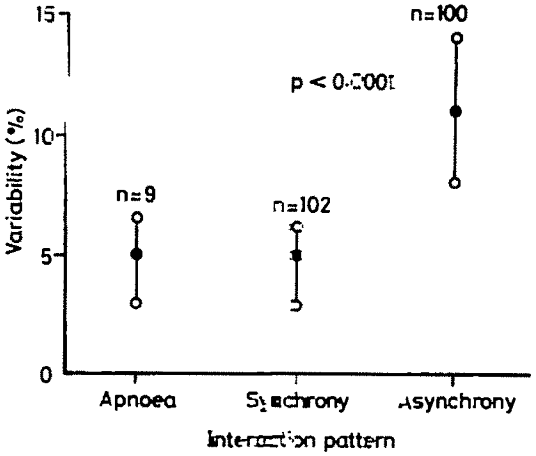

Fig 4 *Plots of median coefficients of variation (interquartile ranges) for each respiratory interaction phase.*

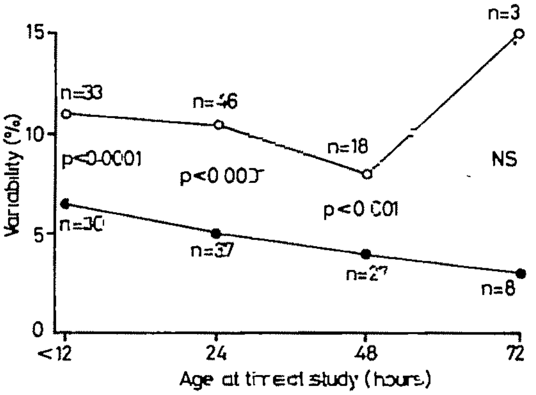

Fig 5 *Plots of median coefficients of variation for synchrony (bottom) and asynchrony (top) subdivided by age at time of study*

## Discussion

The variability in cerebral blood flow velocity of premature babies receiving assisted ventilation was fairly high within 12 hours of birth and fell progressively over the first 48 hours of life. This change was seen during recordings made during both synchronous and asynchronous ventilation (fig 5). These results suggest that variability is greatest at the time when intraventricular haemorrhage usually occurs.[11 12] Drayton and Skidmore suggested that the major intracranial arteries are probably dilated shortly after birth, and that they constrict over the first 48 hours of life in response to rising blood pressure.[13] These authors hypothesised that while the cerebral arteries are dilated they are less efficient at damping arterial pressure surges and thus place the premature infant at particular risk of intraventricular haemorrhage in the early hours of life.

A second explanation for our results is that systemic blood pressure may have fluctuated less after 48 hours of life and that this (rather than any change in the diameter of the cerebral vessels) was responsible. Unfortunately systemic variability of arterial blood pressure could not be monitored as the lumens of the umbilical arterial catheters were too narrow and had side rather than end openings. These catheters result in severe damping of any pressure fluctuations.

This study shows that the pattern of interaction between spontaneous respiration and mechanical ventilation influences the variability of the velocity of blood flow in the major intracranial arteries: apnoea and synchronous breathing result in low variability and asynchronous breathing in significantly higher variability. It is not possible to comment on the association between the pattern of ventilation interaction and the occurence of intraventricular haemorrhage in our small study.

Theoretically, changes in the velocity of blood flow could result either from changes in blood flow or in the calibre of arteries, but the calibre of a vessel is unlikely to change rapidly enough to produce variations in velocity from beat to beat. Experimental evidence exists that suggests that the cerebral vessels with a diameter of over 200 μm that change in calibre during autoregulation at physiological blood pressures take between three and seven seconds to change size.[14 15] It seems most likely that the variations from beat to beat in velocity of the blood flow seen in this study represent actual changes in blood flow. The effects of different patterns of interaction between spontaneous respiration and mechanical ventilation on venous return and cardiac output provide a logical explanation for this. In a subject breathing normally, respiration affects the circulation.[16] During inspiration the intrathoracic pressure falls and blood is drawn into the right side of the heart from the systemic venous circulation leading to a rise in right heart output. At the same time, because the fall in intrathoracic pressure causes dilatation of the pulmonary venous system, return of blood to the left side of the heart is reduced and left heart output falls; this causes a drop in systemic blood pressure. The fluctuations in venous return and arterial blood pressure are fairly small in the healthy subject, but they may be exaggerated by the airways obstruction and hypovolaemia that may occur in sick babies receiving assisted ventilation.

When a baby is subject to asynchronous ventilation the changes in intrathoracic pressure are likely to be greater and more irregular. During asynchrony low intrathoracic pressures and falls in systemic venous and arterial blood pressure will occur when the baby breathes in during the deflation phase of the ventilator, and high intrathoracic pressures (and rises in systemic venous and arterial pressure) will occur when the baby breathes out while the ventilator is attempting to inflate the lungs. This rise is particularly likely if the baby actively expires.[17] If a baby breathes synchronously with the ventilator, then spontaneous breathing in coincides with inflation and the change in intrathoracic pressure is small. Asynchronous breathing would thus result in more erratic and larger flucutations in arterial blood pressure and in venous drainage from the head than synchronous breathing or apnoea.

An increased variation in occipitofrontal circumference during positive pressure ventilation has been reported that presumably reflects changes in cerebral blood volume.[18] Variations in cerebral venous and arterial velocities measured with Doppler ultrasonography also occur in phase with artificial ventilation, and a reduction in peak inspiratory pressure or discontinuation of ventilation reduced the variability in velocity.[19] The greater variability in cerebral blood flow velocity in the early hours of postnatal life could partly explain the usual timing of periventricular heamorrhage.

These results show that asynchronous ventilation leads to greater fluctuations in the velocity of blood flow through the intracranial arteries. If, as suggested by other authors, these fluctuations increase the risk of intraventricular haemorrhage, then measures to reduce the amount of asynchronous ventilation might reduce this risk.

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# Neonatal infection in premature infants and use of human immunoglobulin

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SUMMARY In an open study 120 consecutively admitted premature babies of 32 weeks' gestation or less, were randomised to receive weekly intramuscular injections of human normal immunoglobulin (50 mg/kg). There was no significant difference between the number of babies in the treated and untreated groups who had at least one episode of infection, but the total number of infective episodes was substantially less in the treated group (n=22) compared with 40 in the non-treated group. Three babies died from overwhelming infection and three babies developed necrotising enterocolitis, all in the group that had not been treated. Serum IgG concentrations were significantly higher in the treated group by the age of 2 weeks but remained consistently below those of full term babies of similar postnatal age. Administration of human immunoglobulin may decrease the severity of infection in premature babies, but alternative regimens may be more successful.

Premature babies have low serum immunoglobulin concentrations at birth and do not start producing appreciable amounts of endogenous immunoglobulin until they are at least 15 weeks old.[1] Premature infants of 32 weeks' gestation or less are particularly compromised, their IgG concentrations being liable to fall to 2·0 g/l or less as early as six weeks after birth. A baby born at term at a similar postnatal age has a serum IgG concentration of about 6·0 g/l.[2]

Despite intensive treatment with antibiotics infection remains an important cause of mortality and morbidity in premature babies. This study aimed to determine whether treatment with intramuscular human normal immunoglobulin could decrease either the morbidity or mortality or both, associated with infection in premature infants.

## Patients and methods

One hundred and twenty preterm babies of 32 weeks' gestation or less, who were consecutively admitted to a regional neonatal unit, were randomised to receive human normal immunoglobulin 50 mg/kg intramuscularly weekly (n=59) or remained untreated (n=61) (table 1). (It would have been unethical to have used a double blind protocol in which the control group received weekly placebo intramuscular injections.) The immunoglobulin, which was prepared by the Blood Products Laboratory, Elstree, and issued by the Central Public Health Laboratory, London, was injected into the lateral aspect of the upper thigh. Blood was sampled for IgG within the first 48 hours of life, before transfusion of blood or any blood products, and then every two weeks until discharge on the first 100 babies. Serum IgG concentrations were measured by a standard centrifugal fast analyser (Encore, Baker Instruments)

All clinically suspected episodes of infection and the results of allied investigations (full blood count,

Table 1 *Comparison of groups by gestational age*

| *Gestational age (weeks)* | *No treated with human immunoglobulin (n=59)* | *No not treated with human immunoglobulin (n=61)* |
|---|---|---|
| 24 | 2 | 3 |
| 25 | 1 | 2 |
| 26 | 4 | 6 |
| 27 | 5 | 5 |
| 28 | 8 | 8 |
| 29 | 10 | 8 |
| 30 | 13 | 11 |
| 31 | 8 | 10 |
| 32 | 8 | 8 |

differential white cell count, culture of blood, urine, and cerebrospinal fluid, and chest *x* ray picture), were documented for both groups. The investigations were carried out by junior medical staff whenever a deterioration in an infant's condition could not immediately be explained by an acute episode — for example, a pneumothorax, displacement of the endotracheal tube, or extensive intraventricular haemorrhage. The medical staff were not necessarily aware of whether the baby had been treated or not but such knowledge would probably not have prejudiced the study because the response was to a clinical deterioration in the baby's condition and would have been followed through irrespective of whether the baby had been randomised to receive immunoglobulin or not.

Suspected episodes of infection were, in the light of subsequent information, categorised as infection on clinical criteria alone (category A), infection on clinical criteria with supporting laboratory evidence but without positive blood culture (category B), infection confirmed by positive blood culture (category C), or as not infective if a satisfactory alternative explanation was found for the baby's deterioration.

The Kolmogorov-Smirnov test was used to determine the normality of the data. Subsequent analysis was by Student's *t* test or the Mann-Whitney U test as appropriate

The study was approved by the hospital ethical committee and fully informed parental consent obtained in each case.

## Results

Twelve babies who died within two days of birth and one baby who died when 4 days old (seven in the treatment group and six in the control group) from complications of extreme prematurity (severe intraventricular haemorrhage, severe perinatal asphyxia, pulmonary haemorrhage, pulmonary interstitial emphysema, or pneumothoraces) were not included in the final analysis.

The mean gestational age of the remaining 107 babies was 29·3 weeks (range 24–32), and mean birth weight 1220 g (range 600–2200) Both groups were comparable for gestational age, birth weight, sex, and length of follow up. There were no significant differences between the groups in the incidence of intraventricular haemorrhage, respiratory distress syndrome, maximum inspiratory pressure, maximum inspired oxygen received, number of days of oxygen supplement given, total time of intermittent positive pressure ventilation, number of days of total parenteral nutrition, time to starting oral feeds, or length of time that umbilical artery catheterisation was required.

Three babies of gestational ages 27, 28, and 30 weeks, all in the control group, died of overwhelming infection. Organisms isolated from blood were *Klebsiella pneumoniae* and *Streptococcus faecalis*, coagulase negative staphylococci, and *Escherichia coli*; the babies died on days 37, 19, and 33, respectively. Three babies in the same group developed necrotising enterocolitis. The diagnosis was made clinically and from the characteristic radiological appearance of pneumatosis intestinalis in two cases, and confirmed by laparotomy in the third; one of the babies died of the disease six days after the onset.

On 107 occasions clinical deterioration was thought to be due to infection Confirmatory evidence of infection was absent in 11 instances, and the clinical deterioration was retrospectively attributed to other causes: new and extensive intraventricular haemorrhage (n=4); anaemia (n=4); patent ductus arteriosus (n=1); bronchopulmonary dysplasia (n=1); and metabolic acidosis (n=1). Of the remaining 96 episodes, 34 (35%) were in category A, 16 (17%) in category B (table 2), and 46 (48%) in category C (table 3). By definition the diagnosis of category A infections depended only on a subjective clinical assessment, so these episodes were not included in the subsequent statistical analysis. Details of the number of babies with infection (categories B and C) are shown in table 4.

The proportions of treated and untreated babies who had at least one infective episode in category B

Table 2 *Supporting evidence for clinical diagnosis of infection in category B infections*

| *Age of baby (days)* | *Supporting evidence for clinical diagnosis of infection* |
|---|---|
| 4 | Consolidation on chest *x* ray picture<br>Total neutrophils $0{\cdot}25\times10^9$/l |
| 6 | Total white cell count $42{\cdot}6\times10^9$/l |
| 7 | Consolidation on chest *x* ray picture |
| 10 | Total neutrophils $16{\cdot}6\times10^9$/l |
| 12 | Consolidation on chest *x* ray picture |
| 12 | Total neutrophils $28{\cdot}8\times10^9$/l |
| 14 | Consolidation on chest *x* ray picture |
| 17 | Total white cell count $26{\cdot}4\times10^9$/l |
| 20 | Total neutrophils $21{\cdot}7\times10^9$/l<br>(Shift to left)<br>Consolidation on chest *x* ray picture |
| 20 | Consolidation on chest *x* ray picture |
| 23 | Consolidation on chest *x* ray picture |
| 28 | Consolidation on chest *x* ray picture |
| 30 | Consolidation on chest *x* ray picture |
| 33 | Consolidation on chest *x* ray picture |
| 40 | Consolidation on chest *x* ray picture |
| 43 | Consolidation on chest *x* ray picture |

Table 3 *Organisms isolated from blood in category C infections*

| *Organism isolated* | *No of cases in which isolated* | *Site of isolation* |
|---|---|---|
| Coagulase negative staphylococcus | 29 (5 in one bottle only) | Blood |
| *S faecalis* | 4 (2 in one bottle only) | Blood |
| *Kl pneumoniae* and *S faecalis* | 2 | Blood |
| *Kl pneumoniae* | 2 | Blood |
| *Klebsiella oxytoca* | 1 | Blood |
| *S faecalis* and *Staphylococcus aureus* | 1 | Blood |
| *Enterobacter cloacae* | 3 | Blood |
| *E coli* | 2 | Blood |
| | 1 | Urine |
| *Pseudomonas sp* | 1 | Blood |

Table 4 *Details of episodes of infection in categories B and C*

| | *Total No of babies with at least one infective episode* | *No of infective episodes* | | *Total* |
|---|---|---|---|---|
| | | *Category* | | |
| | | *B* | *C* | |
| Group treated with human immunoglobulin | 13 | 4 | 18 | 22 |
| Group not treated with human immunoglobulin | 21 | 12 | 28 | 40 |

or C were not significantly different (22% and 34%, respectively). Similarly, when categories B and C were analysed separately, there was no significant difference between the two groups in the numbers of babies who had at least one episode of infection. Among babies who did have infection, however (categories B and C), the number of episodes in the group who did not receive immunoglobulin (n=40) was significantly greater compared with the treatment group (n=22), p=0·02. This difference was most pronounced in category C (28 episodes compared with 18). Analysis of all babies showed that 33 (31%) were of 28 weeks' gestation or less. These infants had 69% (p=<0·05) of all category B, and 72% (p=<0·001) of all category C infections.

The mean IgG concentrations at birth were comparable in the two groups. By 2 weeks of age the treatment group had significantly greater IgG concentrations (mean 6·1 g/l) than the control group (mean 5·5 g/l), and this difference increased with time (table 5). None the less the IgG concentrations achieved with treatment fell consistently below those of a normal baby born at term during the first few weeks of life (figure).

Table 5 *Mean serum IgG (g/l) concentrations*

| *Week* | *Group treated with human immunoglobulin* | *Group not treated with human immunoglobulin* | *p Value* |
|---|---|---|---|
| 0 | 5·3 | 5·0 | 0·34 |
| 2 | 6·1 | 5·5 | 0·04 |
| 4 | 4·9 | 4·3 | 0·01 |
| 6 | 4·1 | 3·2 | 0·002 |
| 8 | 3·6 | 2·7 | 0·002 |
| 10 | 3·5 | 2·4 | 0·0002 |
| 12 | 3·5 | 1·8 | 0·0002 |

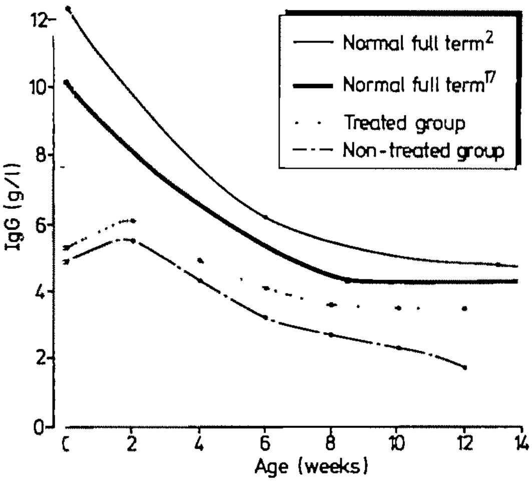

Figure *Serum IgG profile in the newborn: comparison of the study population with babies born at term* [2, 17]

## Discussion

Studies in animals suggest that gammaglobulin may be useful in the treatment of infection. In the late 1940s Cameron reported the therapeutic activity of animal gammaglobulin in infected mice.[3, 4] In the 1950s Fisher showed not only the efficacy of human gammaglobulin against a variety of bacterial pathogens in mice,[5] but also the synergistic effect of gammaglobulin and chloramphenicol, both in doses that had little or no effect when used alone.[6]

There are few studies on the use of immunoglobulin preparations in premature babies and their conclusions are equivocal. In a study of 20 premature infants given 0·5 ml/kg of 16% gammaglobulin about every two weeks for a maximum of four months, Steen found no advantage in treatment, but he did not achieve substantially higher gammaglobulin concentrations in his treated group.[7] Amer *et al* gave a higher dose (3·0 ml/kg in the first week and 1·5 ml/kg at monthly intervals thereafter until the end of the eighth month of life).[8] Of seven deaths from infection, only one was in the treated group. The group receiving gammaglobulin also benefited from treatment in that significantly more of them were free of all clinical infection during the study period and the group as a whole had a lower incidence of minor infection. Although the number of severe infections necessitating admission to hospital was not reduced, the treated group spent less time in hospital. Hobbs and Davies gave 250 mg of pooled adult gammaglobulin to several infants of 33 weeks' gestation or less, and though theirs was not a controlled trial, they suggested that the treatment may have conferred some protection against infection in these premature infants.[9]

There are obvious difficulties in diagnosing infection in neonates. A decision to use antimicrobial treatment is often subjective and not subsequently supported by the results of laboratory investigations. We excluded such episodes of presumed infection (category A) from further analysis. Accurate interpretation of radiological changes in the chest *x* ray pictures of babies requiring assisted ventilation is difficult. When a baby's clinical condition had suddenly deteriorated, however, and in the absence of a mechanical explanation for the observed change, we felt that the appearance of a new confluent shadow was probably due to infection (table 2). Similarly, the result of the neutrophil count may be helpful.[10]

Coagulase negative staphylococci were isolated from 29 (63%) of 46 positive blood cultures (table 3). In 23 (79%) cases they were grown from both blood culture bottles and showed uniform antibiotic sensitivities. This ubiquitous skin commensal cannot easily be dismissed as a contaminant in an immunocompromised group subjected to invasive therapeutic techniques. It is recognised as a major cause of hospital acquired infection in neonatal units and is strongly associated with the use of indwelling catheters in premature babies.[11 12] All our babies had had indwelling venous catheters before developing coagulase negative staphylococcal bacteraemia.

We have shown a substantial difference in the number of infective episodes (22 and 40, p=0·02), deaths from infective causes (0 and 3), and episodes of necrotising enterocolitis (0 and 3) between the group treated with immunoglobulin and the group that remained untreated. There was, however, no significant statistical advantage gained from treatment in terms of the number of babies who had at least one infection of either category B or C, suggesting that the treatment did not decrease the susceptibility of the baby to infection.

A compromised humoral immunity is only one of the potentially correctable immune deficiencies in premature babies. We have studied the effect of supplementation with gammaglobulin alone, a support to just one arm of the immature immune system None the less, IgG accounts for about 80% of the serum immunoglobulin and is the chief component of a baby's serological defence, containing most of the antibacterial, antiviral, antiprotozoal, and antitoxic activity of the serum.[13] Many cells (lymphocytes, macrophages, and killer cells) have receptors for IgG, which can also activate the complement system, promote opsonisation, and participate in antibody dependent cytolytic reactions. Faced with a group deficient in IgG and at high risk of severe infection, therefore, it is necessary to evaluate the full effect of supplementation with gammaglobulin in spite of being aware of other immunological deficiencies.

At times of infection and increased catabolism the IgG concentration may fall precipitously. Greater benefit may be obtained if supplementary immunoglobulin is given concurrently with antibiotics at the onset of a suspected infection.

The IgG concentrations achieved in the treated group were significantly greater than those in the control group but none the less remained substantially less than the IgG complement of a term baby in the first few weeks of life. The infants at greatest risk of infection are those of 28 weeks' gestation or less. It is not practical to inject a greater volume of gammaglobulin into the meagre musculature of these premature babies nor to inject it more often. Alternative regimens using intravenous gammaglobulin preparations that are now available may be more successful; high doses are well tolerated.[14] Hyperimmune preparations may have a role in the prophylaxis of infants at high risk of specific bacterial infection.[15] Effective early treatment of viral infections may also be achieved.[16] We are currently evaluating the possibility that greater protection against infection may result from the rapid achievement and maintenance of IgG concentrations equivalent to those of babies born at term by the administration of intravenous gammaglobulin.

We thank Dr P J Congdon for advice and permission to study his patients, Dr A Milford Ward and the Royal Hallamshire Hospital, Sheffield, for measuring the serum IgG concentrations, Professor R W Smithells for encouragement and advice, Mr A Watkins and Dr A Baines for the statistical analysis, and the regional paediatricians for their cooperation

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## Thirty years ago

### Wheat gluten and coeliac disease

*Claire Alvey Charlotte M Anderson, and Mavis Freeman (Melbourne)—Arch Dis Child* 1957;**32**:434–7

After the identification of wheat flour as the cause of coeliac disease by Dicke in Holland in 1950 the search began for the noxious factor in the flour By 1952–53 it had been confirmed that gluten, the protein fraction of wheat and rye flour, was the cause of the malabsorption. Wheat and rye gluten differ from other cereal proteins in containing more glutamic acid and proline, which can form a type of gel enabling them to be used in breadmaking. The group from Melbourne, noting that the peptide pattern in the gluten molecule is probably associated with the gel property, set out to test the hypothesis that the particular peptide structure of wheat and rye gluten, together with a difference in the enzyme pattern of the patient with coeliac disease, might be responsible for the development of symptoms Various fractions of gluten were tested The phospholipid fraction when extracted and fed to a patient with coeliac disease failed to produce an increase in fat excretion. A tryptic digest of gluten to peptides caused a recurrence of steatorrhoea, while neither an amino acid digest or glutamic acid alone had this effect. Blood glutamine concentrations tested two hours after a dose of gluten were found to be three times higher in patients with coeliac disease than in controls, and Weijers and Van de Kamer had reported similar results from feeding gliadin (the 70% alcohol soluble fraction of gluten)

It was concluded that glutamine itself was not toxic to the patient with coeliac disease but that the toxic fraction was a peptide containing glutamine, and a deficiency of a specific mucosal peptidase that might deaminate the peptide was postulated

**Comment.** In the 30 years since the publication of this paper the development of immunology has radically altered our understanding of many disorders The evidence now points strongly to coeliac disease reflecting an intestinal immune response to gliadin or to peptides from gliadin. The technique of peroral intestinal biopsy was developed by Shiner in 1956, and the characteristic enteropathy of coeliac disease has been shown to be a T cell mediated immune reaction. It has been proposed that lymphocines, secreted by activated T cells, are the mechanism for T cell mediated mucosal damage Other evidence of immunological abnormality is the fact that subjects with isolated IgA deficiency are particularly prone to develop coeliac disease. We are far from a complete understanding of a complex process and, as yet, we do not have any routine laboratory tests for the measurement of intestinal immune reactions

(Charlotte Anderson was one of the first, and possibly the most distinguished, among paediatric gastroenterologists. After making outstanding contributions to the specialty both in Melbourne and in the Chair of Paediatrics in Birmingham she has now retired to her native Australia )

J H HUTCHISON

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# Plasma amino acids in small preterm infants fed on human milk or formula

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SUMMARY Plasma amino acids were measured in 35 preterm infants, of whom 11 weighed less than 1000 g and 24 weighed between 1000 g and 1500 g at the time of sampling. Repeat samples were obtained in 18 at least seven days later. Seventeen infants were fed with preterm formula milk and 18 with expressed maternal breast milk at one to two hourly intervals during the study period. Formula fed infants gained weight faster than those fed on breast milk but there was little difference in amino acid patterns. Infants fed on breast milk were more likely to have concentrations of essential amino acids below the mid trimester fetal range than formula fed infants, but few infants in either feeding group had values above the fetal range. Those that did were equally distributed between both groups. Only two samples approached toxic concentrations, both in the group fed breast milk. The ratio of branched chain to aromatic amino acids was higher in the group fed on formula after correction for post conceptional age, implying that liver maturation may be accelerated by formula feeding. No correlations were found between plasma amino acid concentrations and nitrogen retention or metabolisable energy intake.

The survivals of very small preterm infants are improving all the time. It is common now for babies weighing less than 1000 g at birth to survive, and there is a steadily increasing chance that an infant born weighing less than 750 g will leave hospital well. There are many problems in looking after such babies, not the least being those associated with metabolic immaturity, which makes the type, amount, and route of administration of nutrients critical. Because it is important that infants whose central nervous system is in a state of rapid development should receive adequate nutrition, the clinical management of such babies must strike the right balance between the provision of nutrients in adequate amounts and quality for optimal growth and the possibility of harming the baby by giving more than can be satisfactorily metabolised.[1]

It is still uncertain whether very immature infants are best nourished with their own mothers' milk or with a specially designed formula.[2-4] Preterm mothers' milk may often have quite high protein concentrations,[5] and preterm formulas are designed to have higher protein concentrations than mature breast milk or formulas for full term infants. In either case protein intake by a very immature infant could be too high when fed at the volume of intake generally recommended (180 ml/kg/day), leading to undesirable or dangerous concentrations of potentially toxic amino acids,[6] hyperammonaemia,[7] and metabolic acidosis.[8] Harmful concentrations of one or more amino acids in the blood of a very immature infant can occur without any clinical evidence that the infant is in difficulty, and the smaller and more immature the infant, the more likely are such disturbances to be silent. High plasma concentrations of amino acids have been reported previously in relatively mature preterm infants fed on high protein formulas.[9-11]

Although preterm formulas are now widely used in neonatal nurseries, there are few data on their effects on plasma amino acid concentrations, neither are such data available for very small infants fed on breast milk. The purposes of this study were to examine the range of plasma amino acids in infants of very low weight (<1500 g) and extremely low weight (<1000 g) to find out whether potentially toxic concentrations occurred with breast milk or formula feeding; to try to determine from the plasma aminograms whether there was any evidence of protein malnutrition; and to see if it was possible to find any associations among plasma amino acid patterns and nitrogen balance, energy balance, and growth rate or maturation, or both.

## Patients and methods

We studied 35 preterm infants of whom 11 weighed less than 1000 g and 24 weighed less than 1500 g at the time the first blood sample was taken. All were managed in the neonatal unit at this hospital throughout the study during which 17 were fed on preterm formula milk (15 on SMA LBW, one on Prematalac, and one on Preaptamil), and 18 on expressed breast milk mainly obtained from their mothers. With the exception of three very small infants in the group fed expressed breast milk, no infant was studied until he was on full enteral feeding at an intake of 180–200 ml/kg/day. The three exceptions had been fed expressed breast milk from birth but had not yet reached full enteral intake at the time the first blood sample was taken. Table 1 shows composition of the formulas. The composition of the breast milk was not determined except during balance periods when nitrogen and energy were measured. Feeds of 180–200 ml/kg/day were given by nasogastric tube at one to two hourly intervals

Gestational age was determined from the menstrual history and from the results of ultrasound measurements performed before 20 weeks' gestation. In cases of doubt Dubowitz's postnatal assessment was used but reliance was not placed on this in infants of less than 29 weeks' gestation. None of the infants had any congenital abnormality and none was in a critical condition at the time of blood sampling.

The weights at the times of sampling were obtained from the weight record, all infants being weighed daily on a Marsden spring balance (Marsden Weighing Machines Ltd, London) accurate to within 5 g. The rate of weight gain at each blood sampling date was calculated from the weights recorded for seven to 14 successive days (including the date of sampling) during which the type of feeding was not changed. The line of best fit and the slope representing the rate of weight gain were computed by the method of least squares, and weight gain was expressed as g/kg/day using the median weight as the reference.

Table 1 *Composition of preterm formulas (per litre except osmolality)*

| | *SMA LBW* | *Preaptamil* | *Prematalac* |
|---|---|---|---|
| Protein (g) | 20 | 21 | 24 |
| Fat (g) | 44 | 36 | 50 |
| Saturated (%) | 49 | 47 | 48 |
| Unsaturated (%) | 51 | 53 | 52 |
| Carbohydrate (g) (as disaccharide): | 82 | 83 | 56 |
| Lactose (g) | 41 | 83 | 46 |
| Maltodextrin (g) | 41 | Not given | Not given |
| Energy (kJ) | 335 | 310 | 321 |
| Osmolality (mOsm/kg) | 268 | 350 | 342 |

The blood samples were taken when blood was needed for clinically important investigations. All samples were taken shortly before a feed was due to be given, and never more than two hours after the previous feed. The study had the approval of the hospital ethical committee and the permission of the mothers was obtained before blood sampling.

Blood samples for amino acid analysis were obtained from all infants. In nine infants from each feeding group samples were obtained on a second occasion at least seven days after the first, a total of 53 amino acid profiles being obtained. Most of the blood samples (volume 100–200 µl) were obtained from peripheral veins but in a few cases heel prick samples were used. All samples were taken into heparinised tubes and immediately separated. Plasma was stored at −20°C until deproteinised and analysed.

Protein was removed from the plasma samples overnight at 4°C with 25 mg 5-sulphosalicylic acid/ml of sample. They were then centrifuged at 8800 g for three to four minutes and the supernatants passed through a 0·22 µm millipore membrane before being returned to the −20°C freezer. Centrifugation and millipore filtration were repeated immediately before amino acid analysis. The preferred volume for amino acid analysis was 40 µl, but smaller volumes had to be used in some cases.

Free amino acids were measured in an LKB 4400 automatic analyser (LKB Biochrom Ltd, Cambridge, United Kingdom) using a lithium buffer system. Hamilton amino acid calibration standards (Hamilton Co, Reno, Nevada, United States of America) were used at a concentration of 10 nmol for most residues. Standards were run before and after each batch of four or five samples. Retention times and peak areas were calculated automatically on a Spectra Physics integrator (Spectra Physics, St Albans, Hertfordshire, United Kingdom).

Amino acid residues in both standard and sample amino acid profiles were identified by their order of appearance and amino acid concentrations were calculated from the printout of the peak area provided by the integrator. Proline and hydroxyproline peaks were measured by hand. Glutamine standard was freshly prepared and loaded separately from the mixed amino acid standard because of its poor stability. The glutamine peak area of some standards from which glutamine had been omitted was calculated from the mean ratio of glutamine to six other amino acids (aspartic acid, asparagine, glutamic acid, cysteine, ornithine, and arginine) in the standards where glutamine had been included. The mean interassay coefficient of variation for amino acids at 10 nmol in standards run within the same week and with the same batch of ninhydrin reagent was 6·1% (range 3·1–18·7).

Total amino acids comprise the sum of taurine, threonine, serine, proline, glycine, alanine, citrulline, valine, cysteine, methionine, isoleucine, leucine, tyrosine, phenylalanine, ornithine, lysine, histidine, and arginine Tryptophan could not be measured in our assay. Glutamic acid, glutamine, aspartic acid, and asparagine were not included in the total amino acids because storage and analysis affect their concentrations. It was not always possible to measure hydroxyproline, and most investigators do not report ethanolamine, so these were also omitted from the analysis of total amino acids. Cystathionine was not detectable in most of the samples, so we have not reported the results. Total essential amino acids comprise threonine, valine, methionine, isoleucine, leucine, phenylalanine, lysine, and histidine. Cysteine, arginine, and glycine are considered to be 'semi-essential' amino acids for preterm infants by some authors.[12–14]

In 24 infants (15 fed on formula and nine fed breast milk) energy and nitrogen balances were also performed. Faeces and urine were collected for three days between carmine markers as previously described,[15] stored at −24°C before analysis, freeze dried and homogenised. Energy was calculated by ballistic bomb calorimetry[16] and nitrogen by Kjeldahl analysis (Kjeltec, Tecator AB, Högenäs, Sweden). Samples of feed were also analysed. Nitrogen retention was defined as the difference between nitrogen intake and measured losses in urine and stools, not including integumentous losses which are unknown and likely to be small. Metabolisable energy was defined as the difference between energy intake and measured losses in stools and urine

Comparison of independent samples was carried out by the two tailed Student's *t* test or the Mann-Whitney U test as appropriate. Paired samples were compared by the two tailed Student's paired *t* test or Wilcoxon's matched pairs signed ranks test as appropriate. If significant linear correlations were suspected the regression lines were calculated using the method of least squares. Analysis of covariance comparing formula fed and those fed expressed breast milk for each of the amino acids using birthweight, gestation, and postnatal age as covariates; cluster analysis; and stepwise multiple regression analysis were also performed.

## Results

Table 2 shows the ages and weights of the infants by type of feed. There were significant differences ($p<0·02$) between the postnatal age and weight at sampling of those fed on formula and those fed expressed breast milk, though the mean (SEM) post conceptional age at the time of sampling (gestational age plus postnatal age) was not significantly different being 31·6 (1·9) and 29·9 (2·2), respectively. Smaller and more immature infants were disproportionately over-represented in the group fed expressed breast milk. This was unavoidable because of the need to respect the mother's choice of feeding for her infant, and because of the commonly held view among the nursing staff that expressed breast milk was safer for infants of extremely low birth

Table 2 *Age and weight data of infants studied classified by weight at first blood sampling and by type of feed*

| *Measurement* | *Formula fed (n=17)* | | *Fed on breast milk (n=18)* | |
|---|---|---|---|---|
| | *<1000 g* (n=2)* | *1000–1500 g* (n=15)* | *<1000 g* (n=9)* | *1000–1500 g* (n=9)* |
| Mean birth weight (g) | 795 | 1119 | 870 | 1164 |
| SD | — | 222 | 167 | 149 |
| Range | 690, 900 | 850–1520 | 550–1100 | 940–1460 |
| Mean gestational age (weeks) | 27 | 28·4 | 28·2 | 28·1 |
| SD | — | 2 3 | 2 7 | 1·2 |
| Range | 26, 28 | 25–35 | 25–33 | 27–30 |
| Mean postnatal age at first blood sample (days) | 16 | 24·8 | 9·6 | 16 |
| Range | 13, 19 | 6–48 | 3–29 | 4–36 |
| Mean weight at first blood sample (g) | 810 | 1297 | 859 | 1261 |
| SD | — | 118 | 156 | 146 |
| Range | 740, 880 | 1020–1480 | 500–990 | 1080·1460 |
| Mean weight gain (g/kg/day) | 13·2 | 21·3 | 10·5 | 14 6 |
| Range | 8 8, 17 5 | 10 4–31 6 | −2 24–22·3 | −5·93–25 4 |

*Weight at time of first blood sample

weight. No consistent relation could be found, however, between postnatal age, birthweight, or gestation and amino acid concentrations by multiple regression analysis or by analysis of covariance, except in the case of threonine and methionine. Formula fed infants gained weight significantly faster than those fed on expressed breast milk ($p=0.01$).

All infants weighed less than 1500 g at the time of first sampling. Fifteen infants in the formula group and nine in the group fed expressed breast milk weighed between 1000 and 1500 g at this time; two infants fed on formula and nine fed expressed breast milk weighed less than 1000 g.

Table 3 shows amino acid concentrations (mean and range) in the first blood samples obtained from all infants, compared with the amino acid composition of the main formula. There were few significant differences between the feed groups. Threonine ($p<0.01$) and citrulline ($p<0.05$) were present in greater concentrations in the plasma of formula fed infants than in the plasma of those fed on breast milk. Methionine concentrations were significantly higher in the group fed on formula ($p<0.05$) only when analysis of covariance was performed and not when the uncompensated data were compared. Glutamic acid was higher in the group fed breast milk ($p<0.02$) but because glutamine is easily degraded to glutamic acid when stored the values for these two amino acids tend to be unreliable. Analysis of the sum of glutamine plus glutamic acid showed no significant difference between the groups.

Postnatal age at the time of sampling did not differ between those infants fed on expressed breast milk weighing below 1000 g and those weighing between 1000 and 1500 g (table 2). We found no significant differences in amino acid concentrations between them.

Table 4 shows the highest measured concentrations of those amino acids known to be toxic to immature infants and the ranges found in clinically important hyperaminoacidaemias. Two samples from the group fed breast milk reached the lower end of the clinically important ranges (one for tyrosine, and one for tyrosine and valine). In comparison with Pohlandt's ranges for full term breast fed babies, many infants in our study had raised concentrations of one or more potentially

Table 3 *Amino acid concentrations in $\mu$mol/l, mean (range)*

| *Amino acid* | *Group fed on formula* | | *Group fed breast milk* | | *SMA LBW formula** |
|---|---|---|---|---|---|
| | *<1000 g (n=2)* | *1000–1500 g (n=15)* | *<1000 g (n=9)* | *1000–1500 g (n=9)* | |
| Taurine | 175 (60, 290) | 146 (37–373) | 171 (28–360) | 187 (58–503) | Not given |
| Aspartic acid | 30 (10, 50) | 30 (trace–88) | 31 (trace–85) | 30 (trace–93) | 17 800 |
| Hydroxyproline | 42 (30, 53) | 52 (trace–87) | 41 (trace–133) | 54 (trace–110) | Not given |
| Threonine | 197 (178, 215) | 434 (45–923) | 196 (15–476) | 217 (73–473) | 11 800 |
| Serine | 183 (145, 220) | 238 (58–493) | 200 (81–436) | 244 (75–700) | 13 000 |
| Asparagine | 63 (56, 70) | 78 (46–158) | 63 (trace–105) | 79 (30–168) | Not given |
| Glutamine | 110 (40, 180) | 92 (trace–251) | 233 (39–485) | 159 (48–308) | 31 400 |
| Glutamic acid | 333 (195, 470) | 403 (153–1110) | 259 (112–424) | 466 (249–900) | Not given |
| Proline | 164 (118, 210) | 248 (141–668) | 281 (89–556) | 231 (107–633) | 17 400 |
| Glycine | 224 (218, 230) | 321 (160–688) | 266 (34–504) | 305 (146–625) | 6300 |
| Alanine | 270 (205, 335) | 357 (205–650) | 271 (68–464) | 333 (105–555) | 11 500 |
| Citrulline | 13 (trace, 12·5) | 36 (10–83) | 14 (trace–28) | 26 (trace–83) | Not given |
| Valine | 137 (103, 170) | 170 (96–323) | 168 (62–364) | 144 (68–290) | 12 600 |
| Cysteine | 30 (30 —) | 53 (20–110) | 54 (23–85) | 64 (33–123) | 1500† |
| Methionine | 35 (10, 60) | 36 (10–88) | 25 (4–80) | 24 (trace–45) | 3200 |
| Isoleucine | 26 (13, 40) | 72 (44–119) | 66 (17–148) | 51 (12–123) | 10 500 |
| Leucine | 73 (60, 85) | 126 (70–229) | 116 (47–184) | 99 (35–230) | 18 900 |
| Tyrosine | 57 (28, 85) | 128 (35–258) | 140 (56–320) | 141 (49–393) | 6100 |
| Phenylalanine | 94 (140, 48) | 60 (35–115) | 78 (25–192) | 62 (36–105) | 6500 |
| Ethanolamine | 65 (trace, 55) | 93 (23–165) | 101 (trace–223) | 117 (48–193) | Not given |
| Ornithine | 99 (175, 23) | 138 (53–275) | 81 (37–125) | 164 (45–658) | Not given |
| Lysine | 223 (380, 67) | 180 (120–340) | 126 (33–216) | 156 (75–345) | 14 200 |
| Histidine | 82 (95, 68) | 84 (48–130) | 83 (49–127) | 83 (37–160) | 3300 |
| Arginine | 37 (60, 13) | 50 (16–1081) | 53 (3–116) | 61 (3–128) | 4000 |
| Total | | | | | |
| Essential amino acids | 864 (543, 1185) | 1134 (733–2095) | 855 (373–1708) | 831 (384–1770) | Not given |
| Total amino acids | 2093 (1363, 2823) | 2839 (212–4487) | 2474 (959–4394) | 2569 (1067–5750) | Not given |

*Manufacturer's information, †Value for cystine

Table 4 *Highest measured plasma concentrations of potentially toxic amino acids*

| *Amino acid* | *Highest measured concentration (μmol/l)* | | *Disease range*[25] |
|---|---|---|---|
| | *Formula* | *Expressed breast milk* | |
| Valine | 323 | 364 | 354–646 (classic maple syrup urine disease) |
| Methionine | 88 | 80 | 1930 (cystathione β synthetase deficiency) |
| Isoleucine | 119 | 148 | 168–1366 (classic maple syrup urine disease) |
| Leucine | 229 | 230 | 1107–4000 (classic maple syrup urine disease) |
| Tyrosine | 258 | 393 | 280–2760 (transient neonatal tyrosinaemia) |
| Phenylalanine | 140 | 192 | >1200 (classic phenylketonuria) |
| Histidine | 130 | 160 | 200–1160 (histidinaemia) |

toxic amino acids.[17] There was no difference between the feeding groups in the incidence of high values. When we compared our results with McIntosh's mid trimester fetoscopy values, we found higher values in our study only for methionine (two samples in the group fed on formula) and tyrosine (four samples in the group fed on formula and six in the group fed expressed breast milk).[18]

Low essential amino acids concentrations were found in several infants. Table 5 shows the number of measured values of essential amino acids that were below Pohlandt's[17] and McIntosh's[18] ranges, and the number of infants in whom these low essential amino acids concentrations were measured. Values for glycine were below McIntosh's range in one formula fed infant and three infants fed expressed breast milk.

Whitehead's ratio of essential to non-essential amino acids was calculated from the molar concentrations of glycine plus serine plus glutamic acid plus taurine, divided by those of leucine plus isoleucine plus valine plus methionine, values above 3·0 being commonly found in kwashiorkor.[19] Of the infants in whom the ratio could be calculated, 10 of 17 in the group fed on formula and six of 14 in the group fed expressed breast milk had values above 3·0. The ratio of glycine:valine was also calculated. Values of greater than 2·0 were found in seven of 17 infants in the group fed on formula and in eight of 17 in the group fed expressed breast milk.

The data were examined for correlations which might have been of biological importance. No significant association was found among the following: weight gain and total amino acids, total essential amino acids, valine:glycine ratio, or tyrosine:phenylalanine ratio; postnatal age and valine:glycine ratio, or tyrosine:phenylalanine ratio; nitrogen retention and valine or valine:glycine ratio; or metabolisable energy intake and valine or valine:glycine ratio. Significant correlations were found in both feeding groups between the concentrations of valine, threonine, and total essential

Table 5 *No of low values of essential amino acids in two feeding groups*

| *Amino acid* | *Values below Pohlandt's range for full term breast fed infants*[17] | | *Values below McIntosh's range for mid trimester fetoscopy samples*[18] | |
|---|---|---|---|---|
| | *Formula (n=17)* | *Breast milk (n=18)* | *Formula (n=17)* | *Breast milk (n=18)* |
| Threonine | 1 | 3 | 3 | 9 |
| Valine | 2 | 4 | 9 | 13 |
| Methionine | 2 | 4 | 0 | 2 |
| Isoleucine | 1 | 4 | 1 | 4 |
| Leucine | 2 | 4 | 1 | 4 |
| Phenylalanine | 0 | 0 | 0 | 1 |
| Lysine | 2 | 4 | 8 | 11 |
| Histidine | 0 | 1 | 4 | 9 |
| No of infants with one or more essential amino acids below the stated range | 7 | 9 | 12 | 16 |

amino acids, and the concentrations of total amino acids ($p<0·001$ in each case).

The subgroups of nine infants from each feed group in whom second plasma amino acid analyses were carried out had birth weights and gestational ages that were not significantly different from the remaining infants in their feed group. In the group fed on formula their mean (SD) weights at first and second samplings were 1271 g (182) and 1863 (428), and their median (range) postnatal ages were 18 days (6–48) and 37 days (17–58), respectively. In the group fed breast milk the mean weights were 1126 g (217) and 1633 g (403) and the median (range) postnatal ages were 13 days (7–36), and 42 days (21–67) at first and second samplings, respectively. There were no significant differences in birth weight and gestational age, nor in postnatal age, weight, and rate of weight gain, between these two subgroups at either date of sampling.

In the infants fed on formula hydroxyproline ($p<0·05$) and cysteine ($p=0·05$) concentrations were higher in the first sample than in the second, and taurine was lower ($p<0·05$). In the group fed breast milk citrulline concentration was lower in the first sample than in the second ($p=0·05$), and the valine:glycine ratio was increased in the second sample ($p<0·05$). When all infants in whom more than one sample was analysed were combined (n=18), the comparison of early and late samples showed only two significant differences in amino acid concentrations: taurine was lower in the second sample ($p<0·02$) and the valine:glycine ratio was higher ($p<0·05$). Plasma urea concentration was higher in the first sample than in the second ($p<0·02$).

The association between plasma concentration and postnatal age was examined for four potentially toxic amino acids using data from early and late samples. For methionine, phenylalanine, and histidine there was no clear association between plasma concentrations and postnatal age. There was, however, a pronounced decrease in the median (range) plasma concentration of tyrosine and in variability as postnatal age increased, declining from 160 µmol/litre (27·5–392·5) in infants less than 13 days old (n=8) to 94 µmol/litre (55–105) in infants over 45 days old (n=6).

Glasgow and Moore described the usefulness of the ratio of plasma branched chain amino acids (valine, leucine, and isoleucine) to the aromatic amino acids (tyrosine and phenylalanine) in determining hepatic maturity, because branched chain amino acids are metabolised mainly in muscle and aromatic amino acids are metabolised in the liver, and their plasma concentrations tend to decline as the liver matures.[20] We found no significant correlation between this ratio and post conceptional age in either feeding group or in both groups combined. The mean (SD) ratio was, however, significantly higher in infants fed on formula than in those fed breast milk (1·96 (0·44) and 1·54 (0·40), respectively, $t=2·9$, $p<0·01$), implying greater hepatic maturity among infants fed on formula. When the branched chain amino acids:aromatic amino acids ratio was corrected for post conceptional age to compensate for the shorter gestational period of those fed breast milk, the mean value was still higher in the group fed on formula ($t=2·2$, $p<0·05$).

## Discussion

The overall distribution of the amino acids in our two groups was similar to that reported in other studies of preterm infants (mostly less immature), our values (except for threonine) usually coming within the range of the other published values.

There were surprisingly few differences in the aminograms between the two feeding groups, the main ones being the significantly higher concentrations of methionine (when corrected for age and weight), threonine, and citrulline in the group fed on formula, and of glutamic acid in the group fed expressed breast milk. It is doubtful whether the differences in non-essential amino acids have any biological importance and they are likely to be related mainly to differences in intake. Of greater potential importance was the fact that threonine, methionine (corrected for age and weight), and the sum of the total essential amino acids were significantly higher in the formula fed infants. This may be an advantage or a disadvantage for this group, but these infants were less likely to have values below the range found in the mid trimester fetus (table 5) than were the infants fed expressed breast milk.[18] Rigo et al, showed that threonine metabolism is impaired in preterm infants and advised a restriction of threonine intake to prevent hyperthreoninaemia.[21] In none of our samples, however, did threonine concentrations exceed those found in the mid trimester fetus. We did find two samples in which methionine concentrations exceeded fetal values, but neither came near the range found in diseases associated with hypermethioninaemia. Nevertheless, this finding emphasises the need for caution concerning the methionine content of formulas for very immature infants.

Potentially hazardous rises in amino acid concentrations occur only rarely under normal circumstances, even in the smallest infants (below 1000 g) when the protein intake is below 4 g/kg/day. We found only two samples in which potentially toxic amino acids approached the range of concentrations normally associated with diseases. This finding must be viewed with caution because immature infants, particularly if they have some other metabolic disturbance (such as hypoxaemia or acidosis), might be vulnerable to damage at lower plasma concentrations than are found in mature infants with inborn errors of metabolism. Furthermore, our measurements may have missed the peak postprandial concentrations. It is likely, however, that continued rather than brief and intermittent rises are the most important factors in toxicity, and our results certainly show no evidence of cumulative effects associated with short feeding intervals. It is also reassuring to note that hardly any values exceeded the range of mid trimester fetal values at fetoscopy and analysed in the same laboratory, and those that did were equally distributed between both groups.

Amino acid ratios do not seem to be particularly helpful in determining the state of protein nutrition in very immature infants, in contrast to older infants and children, presumably because plasma concentrations of amino acids in preterm babies are influenced by immature metabolic pathways. Hence Whitehead's essential:non-essential amino acid ratio[19] produced as many 'abnormal' values in the group fed on formula as in the group fed breast milk (and more than were expected from the growth and clinical progress of the babies). The valine:glycine ratio also produced too many 'abnormal' values, and was unhelpful in discriminating small for gestation infants from appropriately grown infants.[22]

No significant differences in plasma amino acid concentrations were shown between very low birthweight and extremely low birthweight infants, though the great variability of amino acid concentrations makes it hard to obtain significant differences without much larger numbers. The longitudinal data showed a decline in taurine concentration in formula fed infants (probably representing its utilisation in the synthesis of bile salts[23]), and the valine:glycine ratio increased, a change that is more likely to reflect enzyme maturation than improvement in protein nutrition.

We found a significant difference in the ratio of branched chain:aromatic amino acids between the two groups, the ratio being higher in the group fed on formula. Glasgow *et al*[20] calculated that this ratio increased with maturation because increasing hepatic metabolism of the aromatic amino acids resulted in lower plasma concentrations in the more mature infants, while the branched chain amino acids changed comparatively little. The higher values of the ratio in our formula fed infants persisted even after correcting for maturity, so there must be some other variable. It is tempting to suggest that formula feeding itself stimulates hepatic maturation. The lower incidence of physiological jaundice in full term formula fed infants in comparison with breast fed infants is well known, but has generally been ascribed to inhibition of conjugation by breast milk rather than to stimulation by formula feeding.

Although certain correlations between weight gain and amino acid concentrations have previously been reported in low birthweight infants—for example, an inverse association between plasma branched chain amino acids and growth velocity[24]—we were unable to show any in our study. We also could not correlate nitrogen retention or metabolisable energy intake with amino acid concentrations. Where the amino acid supply is not limiting growth the plasma concentration will be more likely to reflect individual variability in enzyme maturation and the pathways of metabolism than the relation between supply and demand (for instance the deposition in new tissues). Our results indicate that in very preterm infants plasma amino acids measurements are not useful indicators of protein nutritional state.

Preterm formulas with adapted whey:casein ratios and protein concentrations not exceeding 20 g/l are unlikely to cause dangerous rises in plasma amino acid concentrations when fed at 200 ml/kg/day or less, even in extremely small and immature infants. Moderate rises of some amino acids are as likely to occur when maternal breast milk is used We found no convincing evidence that maternal breast milk was associated with protein deficiency although weight gain was not so fast as on formula feeding, but plasma concentrations of essential amino acids below the fetal range were more likely to occur with breast milk feeding. Until the importance of the immunological properties of breast milk is clarified, particularly with regard to babies nursed in a clean environment, the decision as to whether to use mother's milk (when available) or a preterm formula in these very small infants should be based primarily on the importance of ensuring adequate gut tolerance and on the desirability of maintaining a good rate of growth.

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## *Short reports*

# Cardiovascular collapse after verapamil in supraventricular tachycardia

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SUMMARY Five babies who presented with supraventricular tachycardia were treated with verapamil intravenously. All developed severe hypotension and two died. Verapamil should not be used in the initial management of supraventricular tachycardia in neonates.

Verapamil is commonly used to treat supraventricular tachycardia in children [1] Adverse effects of the drug in infants have been reported[2] but the dangers are still not widely appreciated.

## Case reports

Four boys and a girl with a mean age of 2·6 weeks (range 2–4 weeks) were all born at term after uneventful pregnancies and deliveries. Their mean birth weight was 3170 g (range 2810–3830 g), and they had no neonatal problems until presentation.

### CASE 1

A baby girl developed a supraventricular tachycardia of 300 beats/minute with cardiac failure She was given verapamil 0·3 mg/kg intravenously and five minutes later reverted to sinus rhythm. One hour later she collapsed with a severe bradycardia and despite vigorous resuscitation including administration of calcium gluconate, adrenaline, and dopamine she died. At necropsy the heart was normal

### CASE 2

A baby boy developed cardiac failure secondary to a supraventricular tachycardia of 300 beats/minute. This was reversed by verapamil 0·3 mg/kg given intravenously. A bradycardia immediately developed in association with metabolic acidosis, which responded well to frusemide and sodium bicarbonate given intravenously. A further episode of supraventricular tachycardia was successfully treated with digoxin. He subsequently made a full recovery An electrocardiogram showed no evidence of pre-excitation.

### CASE 3

A baby boy presented with cardiac failure and a supraventricular tachycardia of 300 beats/minute He was given verapamil 0·1 mg/kg intravenously. A few minutes later he became hypotensive and developed a profound bradycardia Atropine was given intravenously resulting in reversion to a supraventricular tachycardia of 330 beats/minute. An echocardiogram showed a dilated, poorly contracting left ventricle The tachycardia persisted even after treatment with digoxin. Five hours after the dose of verapamil propranolol 15 μg/kg was given intravenously and the dose was repeated when he did not respond. He collapsed and developed a profound bradycardia five minutes later, but was successfully resuscitated with calcium gluconate and dopamine given intravenously. After twelve hours the supraventricular tachycardia recurred and was only temporarily terminated with synchronised direct current cardioversion. Permanent conversion to sinus rhythm was achieved with flecainide given intravenously, and he was maintained on oral flecainide. He made a complete recovery and an electrocardiogram was normal.

### CASE 4

A baby boy was admitted with a supraventricular tachycardia of 280 beats/minute and cardiac failure. He received verapamil 0·2 mg/kg intravenously and this dose was repeated after 15 minutes. Despite this the tachycardia persisted, and digoxin 6 μg/kg was given intramuscularly 30 minutes later Within 10 minutes he reverted to sinus rhythm with no evidence of pre-excitation. Two hours later he suddenly became severely hypotensive and required assisted ventilation and plasma, sodium bicarbonate, and frusemide intravenously. The blood pressure returned to normal within six hours and he subsequently recovered

CASE 5

A baby boy presented with cardiac failure in association with a supraventricular tachycardia of 300 beats/minute. Frusemide was given intravenously and digoxin 15 μg/kg orally, with restoration of sinus rhythm. On admission to the regional unit he was still in cardiac failure The electrocardiogram showed signs of Wolff-Parkinson-White syndrome. Shortly afterwards he reverted to a supraventricular tachycardia of 300 beats/minute. He received 10% calcium gluconate 0·3 ml/kg before the administration of verapamil 0·1 mg/kg intravenously without effect, so the dose of verapamil was repeated an hour later. Echocardiography showed a slightly dilated but well contracting left ventricle. The tachycardia persisted and therefore after a further two hours he was given propranolol 1 mg/kg orally. Half an hour later he became hypotensive with a severe bradycardia and failed to respond to resuscitation that included calcium gluconate, adrenaline, and isoprenaline given intravenously. At necropsy an anomalous Kent bundle was found.

## Discussion

The treatment of supraventricular tachycardia can be difficult because a persistent tachycardia may result in depression of myocardial function. With the exception of digoxin, most antiarrhythmics depress myocardial function and cause a further reduction in cardiac output.

Verapamil given intravenously has been advocated as the best drug for the treatment of supraventricular tachycardia.[1] Its side effects, however, (including hypotension and pronounced bradycardia) are well known,[3] and have been reported in infants.[2] Our experience includes two babies who died in the neonatal period and three who made stormy recoveries after developing severe hypotension. Two of these babies received only a small dose of verapamil (0·1 mg/kg).

Calcium gluconate is recommended for the treatment of the haemodynamic complications of verapamil administration.[3] The response to calcium gluconate treatment, however, varies and it is not always successful.[4] Calcium chloride may be more effective than calcium gluconate and this should be available when verapamil is given [5]

The combination of verapamil and propranolol has unpredictable effects on the myocardium. Studies in adults have shown that it is safe if the left ventricle is contracting well but its use in those with impaired contractility is not recommended.[6] These drugs have been used sequentially in the management of resistant supraventricular tachycardia in childhood. Our experience in case 3 shows that even when the interval between their administration is greater than the half life of verapamil, severe myocardial depression can still occur. Case 5 also illustrates that this combination can have disastrous consequences even if there is no impairment of myocardial contractility.

We recommend that verapamil should not be used in the initial treatment of supraventricular tachycardia in neonates and emphasise the dangers of the combination of propranolol and verapamil even if the myocardium is normal and there is a prolonged interval between doses. Synchronised or unsynchronised direct current cardioversion is perhaps the safest method of restoring sinus rhythm, which can then be maintained by digoxin.

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# Cervical spine fractures and rear car seat restraints

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SUMMARY Two cases of potentially fatal cervical spine fractures in children who were inadequately restrained by malfunctioning car seat restraints are presented. Adequate parental maintenance of seat restraints and their readjustment when children change from wearing lightweight to thick, heavy clothing are imperative

Rear car seat restraints are a valuable method of making road travel safer for children. Indeed, the importance of their use has now been emphasised in the *Highway Code*.[1] If these devices are not carefully maintained or the straps not tightened adequately then potentially fatal cervical spine fractures can occur. We report two cases in which inadequate restraint allowed such injuries to be sustained.

## Case 1

A 6 year old boy was wearing a rear seat safety harness when the car in which he was travelling was involved in an accident. The straps of the harness had not been adequately tightened and he slipped forwards and downwards in the harness so that the strap rode up round his neck producing forceful hyperextension. He was unconscious for one minute and was initially unable to move his arms or legs.

Examination in hospital showed bruising with the imprint of the harness buckle under his chin, torticollis, and painful limitation of movement. No abnormal neurological signs were present in the limbs but he had slight difficulty with micturition for several weeks after an initial period of urinary retention lasting 24 hours.

Radiographs of the cervical spine showed a fracture at the junction of both pedicles and lateral masses of C2 (Hangman's fracture). He wore a cervical collar for seven months while undertaking normal activities and this resulted in satisfactory healing with no neurological deficit.

## Case 2

A 16 month old boy was sitting in a British Standard 3254 approved car safety seat which had a non-functioning crutch strap. As a result of a collision he slid down over the faulty leg strap and under the waist straps, (figs 1a and b). His head toppled forward. On examination he had bruising around his neck and chest, with torticollis and limitation of spontaneous movement. There were no abnormal neurological findings.

Initial radiographs were thought to show no fracture, but on subsequent review a fracture through the odontoid peg with displacement on flexion and some compression of the anterior body of C2 were evident. Treatment with a plaster of Paris Minerva jacket for one month and a brace for a further two months produced satisfactory healing and return of full neck movements.

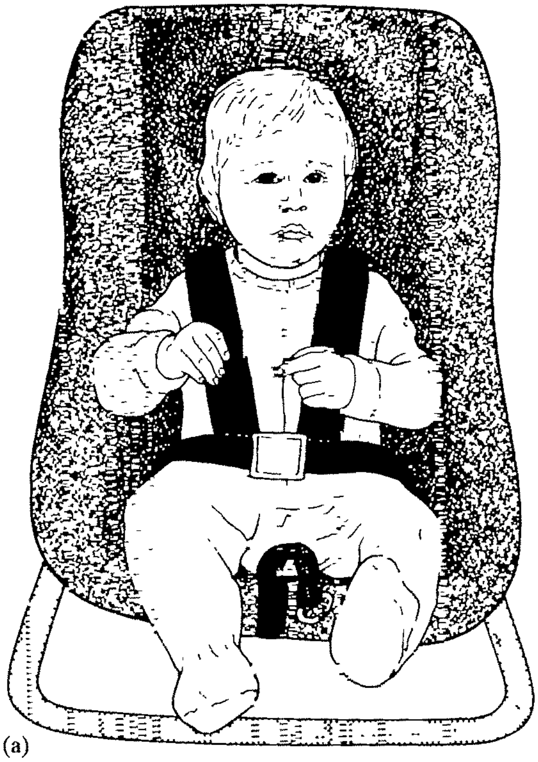
## Discussion

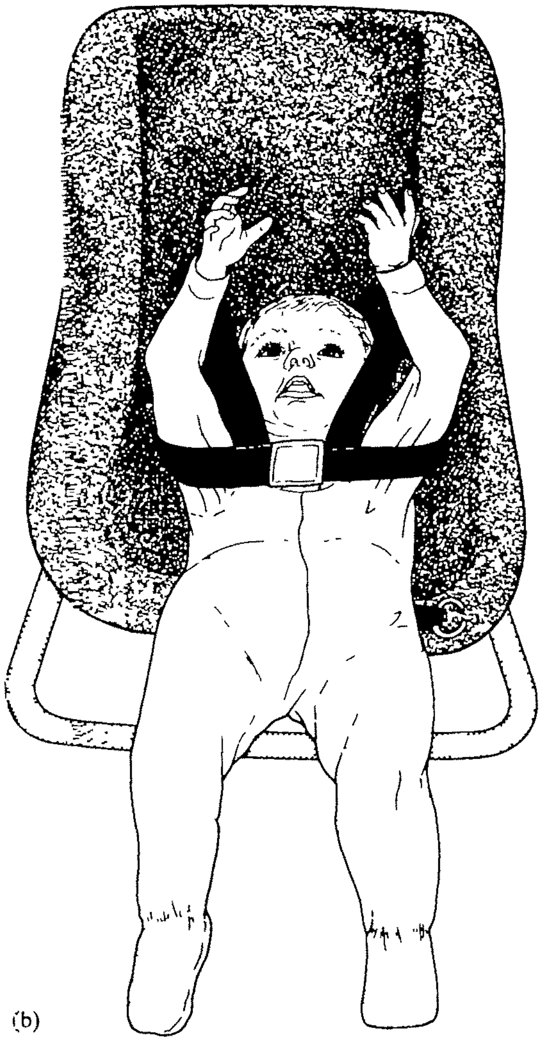
Children who are not wearing restraints are more likely to be seriously injured in car accidents.[2] Restraint by harnesses and car safety seats undoubtedly prevent both deaths and injuries,[3] but such devices are often used incorrectly.[4]

All manufacturers' fitting instructions emphasise the importance of replacing car seat restraints following violent stresses such as road traffic accidents, or if components become worn. Many instructions draw attention to the need for careful individual adjustment of the harness, and some recommend periodic inspection of all anchorage points and harness adjustment devices.

These two cases show that despite this advice parents still fail to adjust the harness adequately and continue to use restraints which are malfunctioning and dangerous. We therefore recommend that all manufacturers explicitly advise periodic inspection by parents of all anchorage points and the harness and locking systems. This may show early abrasion and signs of undue wear which are indications for replacement of the restraint. Parents should also be advised that adjustments to the harness are necessary periodically not only to account for normal growth but also seasonally to account for the changes from light to thick clothing and vice versa.

A design modification to ensure that it is impossible to assemble the locking mechanism *without* incorporating the crutch strap would be useful and would prevent parents continuing to use unsafe car seats as in case two. In addition, use of the currently





Figs 1a and b *Position of child in case 2: a) prior to collision (note crutch strap lying free due to malfunction of locking mechanism), b) following collision (having slid forwards and downwards over useless crutch strap, buckle mechanism is forcefully applied to neck and upper chest)*

less popular types of car seat design which feature the main lock attached to the crutch strap would have prevented the sliding forward movement shown in figs 1a and b.

It is important to emphasise that inadequate parental care and adjustment can transform car seat restraints from a sensible safety precaution into a potentially lethal hazard. We acknowledge that cervical spine fractures in children may be difficult both to diagnose clinically and to see radiologically.[5] Nevertheless clinicians should be aware of the potential dangers of poorly maintained or malfunctioning restraints and not have a false sense of diagnostic security, thereby dismissing injuries in children because they have been sitting in restraints.

We thank Mr J Fissen and Mr E Bryant for allowing us to report these cases, Mrs J Rix for clerical assistance, the department of medical illustration at St Bartholomew's Hospital for the figures, and Ms N Herrera for typing the manuscript.

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# Inspiratory times when weaning from mechanical ventilation

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SUMMARY Two inspiratory times (0·5 and 1·0 seconds) were compared when weaning infants from mechanical ventilation. The shorter inspiratory time was associated with significant increases in minute volume and reduction in active expiration.

The interaction of an infant's spontaneous respiration and intermittent positive pressure ventilation can be an important determinant of outcome; infants who actively breathe out develop pneumothoraces.[1] Both active breathing out[2] and pneumothoraces[3] are more common in infants ventilated with prolonged inspiratory times. Fast rate ventilation (more than 60 breaths/minute) during which the inspiratory time is shortened, reduces the incidence of active breathing out[4] and pneumothoraces.[5]

As the infant is weaned from ventilation the rate is often reduced by increasing both the inspiratory time and expiratory time until the inspiratory time is increased to one second. This increase could stimulate active breathing out and reduce the effectiveness of positive pressure inflation, and might even be responsible for the late occurrence of pneumothoraces. At ventilator rates of 60/minute the inspiratory time is about 0·5 seconds, and infants tend to breathe synchronously,[1] an interaction likely to produce optimum gas exchange.[6] We therefore investigated the hypothesis that a more appropriate method of weaning infants from fast rate ventilation would be to keep the inspiratory time constant at 0·5 seconds and to reduce the rate by extending only the expiratory time.

## Patients and methods

Ten infants were entered into the study; the mean gestational age was 30·1 weeks (range 27–36) and the mean postnatal age 4·3 days (range 3–7). All were receiving assisted ventilation for the respiratory distress syndrome via oral endotracheal tubes using Sechrist ventilators

Permission for this study was given by the hospital ethical committee.

Infants were entered into the study when their respiratory distress syndrome had improved to the extent that at a ventilator rate of 60/minute and an inspiratory time of 0·5 seconds the peak inflating pressure could be reduced to 20 cm $H_2O$ or below. Subsequently no reduction in the peak inflating pressure was made, and the ventilator rate was reduced by increasing only expiratory time, the inspiratory time remaining constant at 0·5 seconds throughout. Examples of ventilator settings are: 40 breaths/minute, inspiratory time 0·5 seconds, expiratory time 1·0 seconds, 20 breaths/minute, inspiratory time 0·5 seconds, expiratory time 2·5 seconds.

During weaning, at ventilator rates of both 20 and 40 breaths/minute inspiratory time was temporarily increased (for 20 minutes) from 0·5 to 1·0 seconds. It was therefore possible to study the infant at two different inspiratory times during weaning. At each ventilator setting recordings were made of transcutaneous oxygen, volume exchange, and the infant's spontaneous respiratory interaction by the method previously described in detail.[1 4]

Transcutaneous oxygen tension was monitored throughout the study Transcutaneous oxygen tensions were reported as the mean of the results of the final five minute period at each inspiratory time and ventilator rate. We analysed the respiratory recordings after a period of up to two minutes had been allowed at each inspiratory time and ventilator rate for the infant to adjust to the new setting. Inflating volume was defined as the volume of gas delivered during positive pressure inflation. Spontaneous respiratory rate and tidal volume were recorded between each positive pressure inflation. Minute volume was calculated as the volume of gas delivered in one minute by both mechanical ventilation and spontaneous respiration. From the recordings at each rate and inspiratory time the amount of active breathing out was determined.[4]

At an inspiratory time of 0·5 and 1·0 seconds and at both ventilator rates the significance of differences in volume exchange was calculated using the Wilcoxon rank sum test. The significance of differences in the presence of active breathing out was calculated using Fisher's exact test.

## Results

The inflating volumes were not significantly different at the two inspiratory times at either ventilator rate When the inspiratory times of 0·5 and 1·0 seconds were compared at both rates there were no

Table *Volume exchange at different inspiratory times (expressed as mean values of 10 patients)*

| *Ventilator rate* | *Inspiratory time at 40 breaths/minute (seconds)* | | *Inspiratory time at 20 breaths/minute (seconds)* | |
|---|---|---|---|---|
| | *0·5* | *1·0* | *0·5* | *1 0* |
| Inflating volume (ml) | 13·1 | 13·8 | 10 8 | 11 3 |
| Spontaneous respiratory rate (minute) | 55 3 | 16·1 | 43 7 | 16 3 |
| Spontaneous tidal volume (ml) | 4·[illegible] | 2·1 | 3 0 | 2 7 |
| Minute volume (ml) | 750 | 628 | 436 | 373 |

significant differences in the spontaneous tidal volumes, but spontaneous respiratory rates ($p<0·01$) and minute volume ($p<0·05$) were significantly greater at the shorter inspiratory time (table).

Transcutaneous oxygen tensions were similar in four infants at the two inspiratory times but in six were higher at the shorter inspiratory time showing a change in oxygenation of greater than 1·33 kPa. In those infants actively breathing out at an inspiratory time of 1·0 seconds oxygenation improved at the shorter inspiratory time. At both rates only one infant made active efforts to breathe out at an inspiratory time of 0·5 seconds but at the longer inspiratory time seven of the 10 infants did so ($p<0·02$).

No infant required a change in peak inflating pressure or ventilator rate, or developed a pneumothorax once weaning had started.

## Discussion

The shorter inspiratory time (0·5 seconds) was not associated with a significant reduction in inflating volume; there are two possible explanations for this. Firstly, at the longer inspiratory time most of the infants breathed out before the end of positive pressure inflation, thereby limiting volume exhange. Secondly, although the infants were recovering from respiratory distress syndrome their lungs were still non-compliant with a reduced time constant, thus 0·5 seconds was long enough to complete volume exchange.

Maintaining a shorter inspiratory time by increasing the time between positive pressure inflations permitted increased respiratory activity, which in turn significantly increased the minute volume, thereby improving gas exchange. Another important advantage of the shorter inspiratory time was that fewer infants actively breathed out.[1]

These results suggest that a shorter inspiratory time may be advantageous and it appears to be safe. It is now important to compare the efficacy of the two methods. We have therefore embarked on a randomised study to assess if (as we predict from these results) the length of weaning is reduced if the inspiratory time is limited to 0·5 seconds.

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# Misdiagnosis of cystic fibrosis

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SUMMARY On reassessment of 179 children who had previously been diagnosed as having cystic fibrosis seven (4%) were found not to have the disease. The importance of an accurate sweat test is emphasised as is the necessity to prove malabsorption or pancreatic abnormality to support the diagnosis of cystic fibrosis.

During the past six years we have provided a referral service for children and adults with cystic fibrosis in the Yorkshire region. They are referred by the consultant undertaking their long term care for a comprehensive assessment.

We describe seven children who had been diagnosed as having cystic fibrosis and who were receiving treatment. The diagnosis was not confirmed and we suggest ways by which such mistakes can be avoided.

## Patients

Table 1 gives details of the seven children who were referred from different district hospitals They had been diagnosed as having cystic fibrosis and treated for periods ranging from five months to eight years. All seven had received daily physiotherapy and six were taking pancreatic supplements and antibiotics regularly. Three were on low fat diets. The commonest reasons for diagnosing cystic fibrosis were recurrent chest infections and failure to thrive. One child had a sibling with cystic fibrosis and another a maternal cousin with the disease.

All seven children were considered to have abnormal sweat tests at the time of the original diagnosis. Four (cases 1–4), however, had at least one equivocal sweat test result. Five children were over the age of 3 when the diagnosis was made. Three children had no gastrointestinal symptoms and of three who had trypsin or chymotrypsin activity estimated in the faeces, only one (case 1) was abnormal.

## Results

Table 2 shows the results obtained during reassessment at our unit. All the children had normal sweat tests with sodium and chloride concentrations of less than 60 mmol/l.

All seven children had chymotrypsin activity estimated in faeces after pancreatic supplements had been stopped and the results were within the normal range (120 μg/g or above). Six children had their faecal fat output estimated and all were normal. Faecal fat output was determined using a non-

Table 1 *Clinical details of children wrongly diagnosed as having cystic fibrosis*

| *Case No* | *Age at initial diagnosis (years)* | *Symptoms* | *Original sweat tests (mmol/l)* | | *Duration of treatment of cystic fibrosis* | *Other factors* |
|---|---|---|---|---|---|---|
| | | | *Sodium* | *Chloride* | | |
| 1 | 9 months | Chest infections | 82 | 30 | 8 years | Low faecal trypsin activity |
| 2 | 1½ | Failure to thrive, chronic diarrhoea, abdominal distension | 98<br>56 | 65<br>37 | 2 years 8 months | Mental handicap |
| 3 | 3 | Failure to thrive, recurrent chest infections; offensive stools | 62<br>88<br>75 | 46<br>67<br>55 | 4 years | Maternal cousin had cystic fibrosis |
| 4 | 3½ | Failure to thrive, recurrent chest infections | 67<br>70<br>53 | 68<br>57<br>32 | 5 years 6 months | — |
| 5 | 3½ | Recurrent chest infections, persistent cough | 80<br>109 | 66<br>77 | 3 months | — |
| 6 | 4 | Underweight, recurrent abdominal pain | 119 | 96 | 3½ years | Sibling had cystic fibrosis |
| 7 | 7 | Recurrent chest infections, offensive stools, underweight | 130<br>175 | 115<br>117 | 3 months | — |

Table 2 *Results of reassessment of children wrongly diagnosed as having cystic fibrosis*

| *Case No* | *Sweat tests (mmol/l)* | | *Faecal chymotrypsin activity µg/g* | *Faecal fat excretion gm/day* | *Result of ultrasonography of pancreas* | *Vitamins (µmol/l)* | | *Suspected diagnosis* |
|---|---|---|---|---|---|---|---|---|
| | *Sodium* | *Chloride* | | | | *A* | *E* | |
| 1 | 45<br>32 | 29<br>23 | 225<br>188<br>225 | 2·0 | Not done | 2·4 | 25 | Asthma |
| 2 | 32<br>35 | 24<br>24 | 530 | Not done | Pancreas not visualised | 1·14 | 14·7 | Failure to thrive, mental handicap |
| 3 | 33<br>48 | 29<br>28 | 370 | 0·9 | Mildly abnormal | 5·1 | 41 | Asthma |
| 4 | 48 | 29 | 120 | 3·0 | Normal | 1·5 | 12·3 | Failure to thrive, recurrent chest infections |
| 5 | 30<br>32 | 16<br>11 | 725 | 2·7 | Normal | 1·4 | 22·3 | Recurrent chest infections |
| 6 | 56<br>13 | 50<br>40 | 210<br>810 | 1·7 | Normal | 1·5 | 9·5 | Normal child |
| 7 | 14<br>38 | 29<br>47 | 230<br>520 | 1·1 | Normal | 3·42 | 24·3 | Small asthmatic child |
| Normal ranges | <60 | <60 | >120 | <5g | Normal | 2·83 (1·8) mean (SD) | 17·6 (4·0) | |

absorbable faecal marker, polyethylene glycol 4000, (250 mg or 500 mg three times daily for seven days). Fat and polyethylene glycol were estimated in the stools collected on days 6 and 7, and the daily faecal fat then corrected to the equivalent of 750 mg or 1500 mg of polyethylene glycol daily. Although in five cases this was done while the children were taking pancreatic supplements (case 7 was not receiving pancreatic supplements) their outputs of fat were low and not characteristic of patients with cystic fibrosis receiving treatment. Five children had ultrasound examinations of the pancreas of which only one was possibly abnormal. Fat soluble vitamin concentrations were estimated in all seven patients after they had fasted and omitted their daily supplements. Five had mean (SD) vitamin E concentrations well within the normal range (17·6 (4·0) µmol/l) and all seven had mean (SD) vitamin A concentrations within the normal range (2·83 (1·8) µmol/l). Although the children were receiving routine vitamin supplements none was taking more than 4000 IU of vitamin A daily and none was taking supplementary vitamin E.

The commonest suspected final diagnosis was asthma. In each case the referring paediatrician and the parents were told that the child did not have cystic fibrosis. In the two cases in which there was a family history of the disease the parents refused to accept the reversal of the diagnosis. The parents of one child who had received considerable welfare benefits and a trip to Disneyland in Florida because she had cystic fibrosis attempted to sue the referring paediatrician. When they finally accepted the reversal of the diagnosis the child featured in a daily newspaper article which proclaimed that she had been cured of cystic fibrosis. The mother of the other child transferred his care to another paediatrician. Both children had been admitted to hospital on several occasions and one of them had been treated with an aminoglycoside intravenously.

## Discussion

These seven children were incorrectly diagnosed as having cystic fibrosis because of initially abnormal sweat tests, respiratory tract symptoms, and other suggestive features. All sweat tests were normal when they were repeated at the regional referral unit, and a combination of indirect tests of pancreatic function strongly suggested that there was no pancreatic insufficiency.

Misdiagnosis of cystic fibrosis has been previously reported by Smalley *et al* in 14 children because of initially abnormal sweat tests.[1] They emphasised the importance of testing pancreatic function in the absence of typical clinical features. David *et al* reported seven patients in whom cystic fibrosis had been wrongly diagnosed, but surprisingly only three had abnormal initial sweat tests.[2]

Although a stimulated pancreatic function test using intravenous pancreozymin and secretin is the definitive test for confirming normal pancreatic function, there are several non-invasive methods which have reduced the need for this.[3]

Chymotrypsin activity in faeces is usually low in untreated patients with cystic fibrosis at any age. It is more stable than trypsin in the faeces and less likely to result in false low values. Faecal collections for fat estimation are difficult but are essential if malabsorption of fat is to be proved. The diagnosis should be questioned if the faecal fat output is normal. Estimation of the concentrations of fat soluble vitamins is another useful indirect method of indicating the presence of a gastrointestinal lesion. In a previous study 28 of 30 children with cystic fibrosis who were not receiving vitamin E supplements had plasma concentrations more than two standard deviations below the control mean.[4] In virtually all children with cystic fibrosis over the age of five years the pancreas looks abnormal on ultrasonography.

Although 5–10% of patients with cystic fibrosis do not have clinical pancreatic dysfunction, 5–10% have mild and 85% have severe pancreatic disease.[5] The fact that the pancreatic function tests, although indirect, were normal in our patients is strong evidence against a gastrointestinal lesion and therefore the diagnosis of cystic fibrosis.

The most common diagnostic error is the uncritical acceptance of an abnormal sweat test. It is important that this test is performed by a laboratory used to carrying out the investigation and that the results are interpreted correctly in the light of the patient's age, clinical findings, and additional investigations. It is also important to analyse the chloride as well as the sodium content of the sweat, as in patients with cystic fibrosis whose sweat electrolytes are equivocal (50–70 mmol/l) the chloride concentration is usually higher than the sodium concentration, whereas in normal subjects the reverse is the case.[6]

The implications of an incorrect diagnosis of cystic fibrosis can be extensive, the children receiving unnecessary treatment and investigations. In addition to the anxiety generated by such a diagnosis and worries regarding the child's future, there are genetic implications that may influence decisions about further pregnancies.

It is important, therefore, to reconsider the diagnosis where typical clinical features are either not present or only mild, and to have two reliable sweat tests as well as evidence of malabsorption or pancreatic abnormality (preferably both). We suggest that the sweat test should be repeated and the diagnosis reviewed in all patients with cystic fibrosis about one year after the initial diagnosis. Evaluation of problems in diagnosis is an important function of a cystic fibrosis referral centre.

We thank the department of chemical pathology for the excellent sweat tests

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# Cerebral arteriovenous malformation in a neonate: treatment by embolisation

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SUMMARY A neonate with an aneurysm of the vein of Galen was treated by embolisation using Gianturco coils Doppler ultrasound examination showed that blood flow in the internal carotid artery decreased while that in the pericallosal artery increased after occlusion, suggesting a 'steal phenomenon' with blood directed preferentially towards the aneurysm.

Aneurysm of the vein of Galen presenting with congestive heart failure during the neonatal period is rare but carries a high mortality.[1 2] Stanbridge *et al* reported that the diagnosis could be made non-invasively by two dimensional echocardiography and cerebral ultrasound.[2] Surgical intervention[3] or embolisation under neuro-radiological guidance has been used in older children and adults but outcome in the neonate has been almost universally disappointing. Mickle and Quisling reported a new non-surgical technique of transtorcular embolisation, but had a disappointing result in neonates.[4]

We report the case of a neonate with an aneurysm that was successfully occluded using Gianturco coils.[5] Cerebral blood flow, cardiac output, and flow within the aneurysm were measured before and after treatment using pulsed Doppler ultrasonography.

## Case report

A baby girl born at term weighing 2800 g developed congestive heart failure on the third day. Clinically she had an active praecordium prominent pulsation of the neck vessels and a faint bruit over the anterior fontanelle. Two dimensional echocardiography showed a structurally normal heart with dilatation of the ascending aorta and of the superior vena cava. Cerebral ultrasound examination showed an aneurysm of the vein of Galen that was seen as a large echo free space, 2 cm×2 cm, lying centrally and posterior to the third ventricle. Turbulent blood flow within the defect was detected by pulsed Doppler ultrasonography. Aortic arch angiography and computed tomography scanning with contrast confirmed the diagnosis (figure). Her congestive heart failure was partially controlled by digoxin and diuretics. Subsequently embolisation with Gianturco occluding emboli[5] was carried out by retrograde insertion of the coils through an occipital burr hole, along the straight sinus, and into the aneurysm. These helical stainless steel coils are 5 cm long with thrombogenic Dacron wool filaments embedded along a 4 cm length from the distal tip and are designed for arterial occlusion. This procedure took place in two steps. Initially 15 coils were placed in the aneurysm at the age of 18 days, and three weeks later a further nine coils were inserted to occlude the aneurysm completely.

Postoperatively her clinical recovery was rapid, the cranial bruit disappeared, and medical treatment for the heart failure was stopped. After embolisation pulsed Doppler ultrasound examination showed the absence of flow within the aneurysm suggesting occlusion of the defect. At the age of 21 months she seemed to be developing normally, her head circumference growing along the 50th centile. Repeat ultrasound scans showed no cerebral ventricular dilatation.

Cerebral blood flow was estimated by Doppler ultrasound before and after embolisation (table) using peak systolic velocity and area under the curve in the pericallosal and internal carotid arteries. Cardiac output from the ascending aorta was also measured using pulsed Doppler ultrasonography before and after treatment

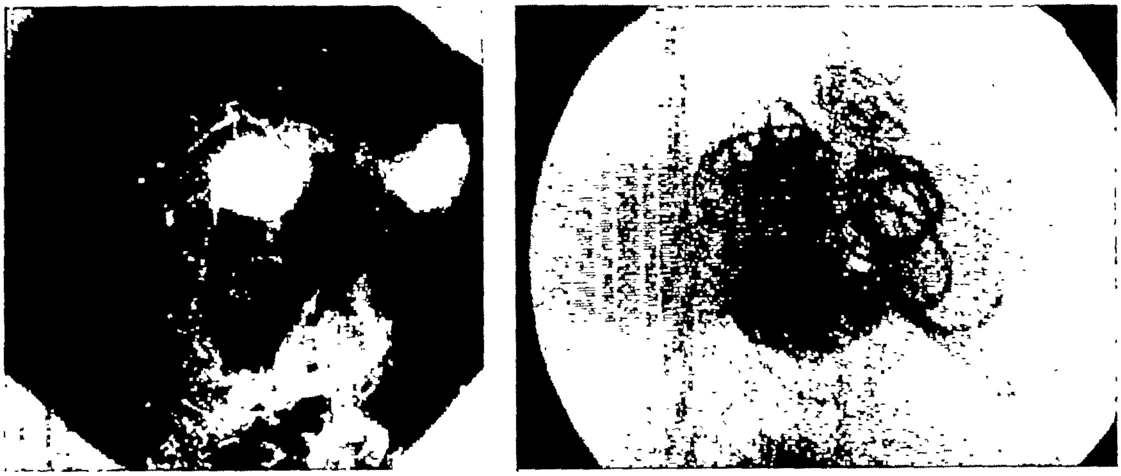

Figure *Left: angiographic contrast image of aneurysm of vein of Galen (centre); drainage is posteriorly towards the torcula (right). Right intraoperative fluoroscopic image (enlarged) showing introducer in situ and position of the Gianturco coils within aneurysm*

Table *Doppler ultrasound measurements of cerebral blood flow before and after occlusion of the arteriovenous aneurysm*

| *Measurement* | *Before occlusion* | *After occlusion* | *% Change* |
|---|---|---|---|
| Peak systolic velocity (cm/second). | | | |
| Internal carotid artery | 109 | 56 | −49 |
| Pericallosal artery | 16 | 39 | +144 |
| Area under the curve (planimeter units/minute) | | | |
| Internal carotid artery | 282 | 191 | −32 |
| Pericallosal artery | 136 | 341 | +151 |
| Cardiac output (ml/kg/minute) | 495 | 29 | −41 |

After treatment there was a substantial reduction in flow through the internal carotid arteries feeding the arteriovenous malformation and increased flow in the pericallosal arteries. After embolisation the cardiac output fell by 41% from 495 ml/kg/minute to 291 ml/kg/minute.

## Discussion

Aneurysm of the vein of Galen is a rare cause of congestive cardiac failure in the neonatal period. Auscultation of a cranial bruit can hasten diagnosis, but this finding is not invariably present. Jeideikin *et al*, in a review of 12 cases, noted that a cranial bruit was present at initial diagnosis in only two (17%) but at some time during life was heard in 75%.[6]

To our knowledge this is the first report of successful retrograde embolisation of an aneurysm of the vein of Galen in a neonate using Gianturco coils. Previous reports have indicated a uniformly poor outcome of affected neonates, whether treated or not, with a high incidence of neurological handicap in the few survivors. In this case nonsurgical treatment resulted in a good outcome, growth and development being normal at the age of 21 months.

Our Doppler haemodynamic findings suggest the presence of a 'steal phenomenon', with blood directed preferentially towards the malformation with a low vascular resistance and away from other areas of the brain. This steal phenomenon may be the cause of the ischaemic brain lesions found at necropsy by Norman and Becker in their series of seven neonates with aneurysms of the vein of Galen (cerebral infarction n=2; periventricular leucomalacia n=5; and haemorrhagic infarction n=2).[1]

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# Tight nuchal cord and neonatal hypovolaemic shock

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SUMMARY Two neonates who went into acute hypovolaemic shock due to a tight nuchal cord were successfully resuscitated. The occurrence of this life threatening complication in two low risk pregnancies emphasises the importance of having staff trained in resuscitation immediately available in the delivery unit.

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Cord entanglement occurs in about 20% of all deliveries,[1 2] and is associated with anomalies of fetal heart rate during labour, and perinatal asphyxia.[1 3 4] Recently neonatal anaemia, usually asymptomatic, was reported as a complication of even a loose nuchal cord[2]

This paper describes two mature infants with life threatening hypovolaemic shock caused by a tight nuchal cord and no other obstetric complications.

## Case reports

### CASE 1

A baby boy weighing 3330 g was born at term after an uneventful pregnancy. The mother was 36 years old, healthy, normotensive, and nulliparous. Spontaneous labour was followed by spontaneous rupture of membranes and the liqour was clear. Epidural anaesthesia (10 ml 0·25% bupivacaine for six hours) was started during labour and the blood pressure remained stable. The second stage was augmented with oxytocin (4 mU/minute for 50 minutes). The cardiotocograph showed early (type I) decelerations, later irregular (type III), and late (type II) decelerations, but there was no fetal acidosis (the pH of the scalp blood was 7·34). Vaginal delivery was assisted by easy elective vacuum extraction. At birth a single loop of cord was tightly wound round the infant's neck and cord transection was required for further delivery. The Apgar scores were 4 at one and five minutes The pH of the umbilical artery blood was 7·33.

The infant was extremely hypotonic and pale, with a tachycardia. The peripheral pulses were weak, and there were signs of poor capillary perfusion. There was no oedema or splenohepatomegaly. Five minutes after birth the pH of the infant's blood was 7·05 He was immediately intubated and 50 ml of plasma given through a venous umbilical catheter in the delivery room. Shortly afterwards 75 ml of whole blood was transfused because of the suspicion of acute fetal blood loss. Venous haematocrit before the blood transfusion was 33%. Examination of a peripheral blood smear showed a normochromic normocytic anaemia (haemoglobin concentration 90 g/l) without normoblastosis. A few hours after the blood transfusion the child was extubated and 48 hours later he was transferred to the postnatal ward, from which he was discharged in good health when 6 days old.

In this case there was no fetomaternal blood group incompatibility and the direct Coombs' test was negative. The placenta (700 g) and the umbilical cord (length 42 cm) were normal. Cord insertion was paramarginal without aberrant vessels. Fetal membranes were complete and there were no blood clots on the maternal surface of the placenta. Fetomaternal transfusion was excluded because the Kleihauer test performed six hours after delivery was negative. The infant had no signs of external or internal haemorrhage. Ultrasound and computed tomography scans of the brain and abdominal ultrasound examination yielded normal results.

### CASE 2

A baby boy weighing 3010 g was born at a gestational age of 38 weeks. The mother was 29 years old, healthy, normotensive and multiparous. The cervix was softened by extra-amniotic instillation of prostaglandin $E_2$ gel, and low amniotomy was performed two hours before delivery. The liquor was clear. Epidural anaesthesia (12 ml 0·25% bupivacaine for one hour) was started during labour and blood pressure remained normal. The second stage was augmented with oxytocin (6 mU/minute). Internal monitoring showed early (type I) and late (type II) decelerations. Five minutes before birth the pH of the scalp blood was 7·31. The infant's head was delivered easily by ventouse but the neck was tightly entangled by two loops of cord. Because the nuchal cord could not be reduced early clamping and cutting were necessary for full delivery Apgar scores were 4 and 6 after one and five minutes, respectively. The umbilical arterial pH was 7·05.

Because of hypotonia and obvious pallor the infant was transferred to the neonatal intensive care unit. Within the first hour of life rapid deterioration ensued with tachycardia, hypotonia, poor peripheral perfusion, extreme pallor, and continuous grunting. The arterial pulses were undetectable and the blood pressure was 30/15 mm Hg. Because of threatening apnoea the infant was immediately intubated and ventilated, but without improvement. A bolus injection of 30 ml plasma was given, and 60 ml of whole blood was transfused 40 minutes after delivery Just before the transfusion the baby's arterial pH was 6·9. The extreme acidosis was corrected quickly by restoration of the circulating blood volume 15 minutes after transfusion (pH 7·32); this led to considerable improvement in his general condition. The venous haematocrit was 32% before and 45% after the blood transfusion. Further progress was normal and the baby was discharged in good health when he was 5 days old.

As in the first case, investigations to detect the underlying cause of the acute fetal intrapartum haemorrhage were not helpful. Blood group isoimmunisation was excluded. The placenta (650 g) was complete and there was no retroplacental haematoma. No aberrant or ruptured blood vessels were found in the umbilical cord, which was 50 cm long. The Kleihauer test was negative, excluding fetomaternal haemorrhage. There was no obstetric trauma, and ultrasound examination of the neonate's abdomen and brain and computed tomography scan of his head showed no abnormalities. Thus only fetoplacental haemorrhage due to a tight nuchal cord could explain his acute hypovolaemic shock.

## Discussion

When acute fetal blood loss occurs it is usually during labour or delivery.[5] Whatever the underlying cause the clinical picture in the newborn is usually characteristic comprising pallor, tachycardia accompanied by irregular respirations or gasping, weak peripheral pulses, hypotension, and acidaemia. Cyanosis is minimal and the infant's colour is not improved by administration of oxygen. Initially haematocrit and haemoglobin concentrations may be normal (or even misleadingly high) if haemoglobin has been measured in capillary blood samples from an infant in shock owing to peripheral stasis. After equilibration between intravascular and extravascular spaces is reached, however, the expected fall due to the haemodilution and anaemia may show itself.[5]

A peripheral blood smear provides valuable information about the true nature of the anaemia, which is normochromic and normocytic without normoblastosis.[5] These physical and haematological findings are in sharp contrast to those found in neonates with chronic fetal blood loss or perinatal asphyxia whose pallor may be equally severe.

Fetomaternal haemorrhage of sufficient magnitude to result in anaemia at birth was ruled out by the negative Kleihauer test, and internal haemorrhage or iatrogenic blood loss could also be excluded. In the absence of vaginal spotting and after careful examination of the placenta and cord that showed no anomalies that could pinpoint the site of blood loss, fetoplacental haemorrhage due to tight nuchal cord was considered to be the explanation of the condition in both infants.

Cashore and Usher reported neonatal hypovolaemia as a result of tight nuchal coiling.[6] Blood volume determination using $I^{125}$ albumin has shown that this can deprive the infant of up to 20% of its circulating blood volume. In a prospective study on the relation between neonatal anaemia and the presence of either a tight or loose nuchal cord, Shepherd *et al* found that five of 27 (19%) neonates with a tight nuchal cord and four of 30 (13%) with a loose cord were anaemic (haemoglobin concentration less than 132 g/l) within the first 24 hours after birth; no anaemia was found in the patients who served as controls.[2] The authors suggested that the aetiology of the anaemia was cord compression: the blood flow in the thin walled umbilical vein was initially obstructed while the infant's blood continued to return to the placenta through the more muscular umbilical arteries, so that the infant was literally 'pumped out'. Unlike our two patients, these infants were not severely affected by their blood loss

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# Dominantly inherited glomerulonephritis and an unusual skin disease

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SUMMARY An unusual association of uncommon facies including telangiectasia in a butterfly distribution, a similar skin lesion on extensor areas, sparse hair, and membranoproliferative glomerulonephritis is described in a 4 year old boy and his father. The mode of inheritance of these features seems to be autosomal dominant.

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A family is described in which the father and his only son have an unusual association of anomalies. These comprise facial telangiectasia in a pattern not described in other syndromes; telangiectasia of some extensor surfaces; sparse hair, eyebrows, and eyelashes; and membranoproliferative glomerulonephritis. These features seem to be inherited in an autosomal dominant fashion, and after an exhaustive search we can find no evidence that this association has been previously described.

## Case report

A 4 year old boy admitted for tonsillectomy and adenoidectomy was found on routine urine testing to have mild proteinuria and microscopic haematuria. There had been no frank haematuria but on two occasions his urine had been pink. He had no dysuria. Two months previously he had had several undiagnosed febrile illnesses An audiogram performed four months earlier was normal.

He was born at term by caesarean section following a normal pregnancy, and weighed 3200 g. A pyloromyotomy had been performed for pyloric

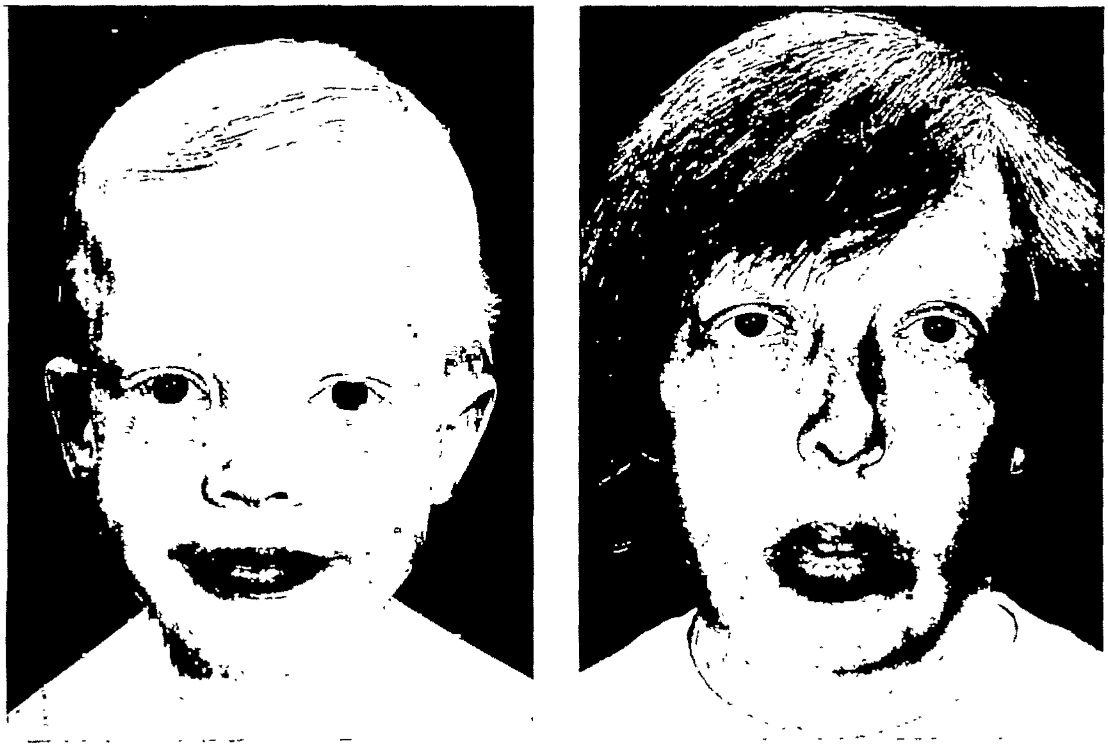

Fig 1 *Facial appearances of father and son showing characteristic features.*

stenosis when he was 1 month old. Subsequent development had been normal.

Family history showed that his parents were unrelated, but his father had end stage renal failure and was hypertensive. He also had a dermatological disease of uncertain aetiology that was similar to the skin lesion of the Rothmund-Thomson syndrome. The father's disease had been diagnosed at 22 years of age and a renal biopsy had been performed eight years later by which time he had been in end stage renal failure. The biopsy specimen showed features of end stage kidney disease which could have been either membranoproliferative glomerulonephritis or focal segmental glomerulosclerosis. Electron microscopy pictures showed focal subendothelial deposits of electron dense granular material, but no evidence of Alport's nephritis. When he was 33 years old he had undergone renal transplantation.

Physical examination of the son showed a well grown boy, on the 50th centile for weight and the 25th for height, with a striking facial appearance closely resembling his father's (fig 1). He had epicanthic folds, hypertelorism, and fine photosensitive telangiectasia in a butterfly pattern on the upper cheeks. Similar telangiectasia was also present on the dorsal aspects of his fingers and elbows. He had blue eyes; pale, fine, short eyebrows and eyelashes, and sparse blonde hair of normal texture with a receding hairline. His mouth, teeth, and nails were normal. He was normotensive, no renal masses were palpable, and both testes were descended.

Analysis of a midstream specimen of urine consistently showed 9–50 red cells per high power field, and protein concentration varied from negative to +++ on Albustix testing. The urinary albumin: creatinine ratio varied from 0·5 to 1·99 (normal <0·1). Antistreptolysin and antideoxyribonuclease titres were within normal limits. Hepatitis B surface antigen screening was negative as were tests for autoantibodies and C3 nephritic factor. Coagulation studies, immunoglobulin concentrations, C3, C4, and $CH_{50}$ activity, chromosome analysis, and renal ultrasonography were normal. Plasma creatinine concentrations were consistently mildly raised (55–

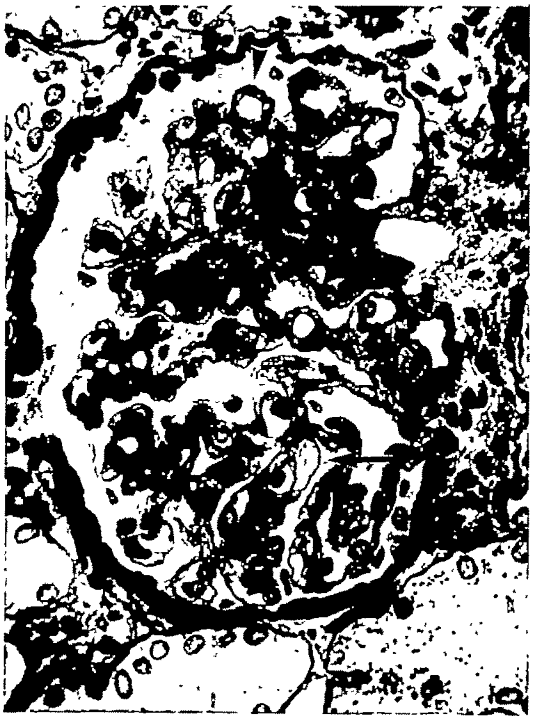

Fig 2a *Glomerulus shows diffuse mesangial proliferation with many double contours (arrow head) and subendothelial deposits (arrow) (Methenamine silver )*

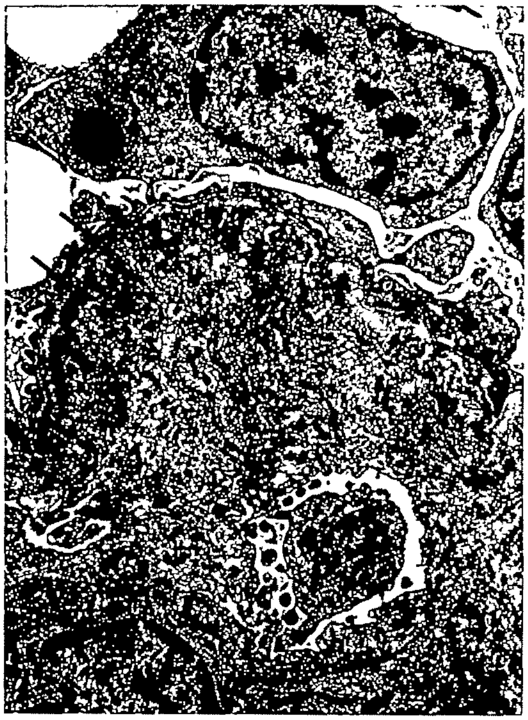

Fig 2b *Single capillary loop with severely narrowed lumen (bottom), mesangial interposition between basement membrane and endothelium, electron dense deposits (arrows) beneath basement membrane, with fusion of overlying epithelial foot processes (Electron photomicrograph.)*

96 µmol/l) but the glomerular filtration rate was 140 ml/minute/1·73m$^2$. Renal biopsy was undertaken at the age of 5 years and 2 months.

The biopsy specimen contained 70 glomeruli which were uniformly abnormal (fig 2a) and although not enlarged showed diffuse mesangial proliferative change Capillary loops were thickened with 'double contour' formation on silver staining and subendothelial deposits were seen. The glomerular changes were accompanied by a mild degree of tubular atrophy and a localised increase in interstitial connective tissue Blood vessels were normal.

Immunofluorescence of IgA, IgG, IgM, Clq, C3, and fibrin was negative and electron microscopy (fig 2b) showed mesangial interposition causing severe narrowing of capillary loops. There were widespread subendothelial deposits, some extremely large, and a moderate fusion of epithelial foot processes. Membranoproliferative glomerulonephritis of subendothelial deposit type was diagnosed.

## Discussion

This unusual association of dermatological abnormality and renal disease, inherited in an apparently dominant manner, does not seem to be well known. The precise nature of the dermatological lesion is still in some doubt; it is similar to the telangiectasia seen in Rothmund-Thomson syndrome but there was no evidence in the child or his father of the characteristic depigmentation and atrophy.[1] A similar photosensitive facial telangiectasia in a butterfly distribution occurs in Bloom's syndrome, in which there is a disorder of DNA stability.[2] Chromosome studies in this patient failed to show any abnormality. Cockayne's syndrome also has a similar facial dermatological lesion and may have associated renal disease, but histological examination of renal biopsy specimens in these patients showed hyalinisation of glomeruli, tubular atrophy and interstitial fibrosis.[3] The other typical clinical features of these conditions were not apparent in the patient or his father The mode of inheritance in Rothmund-Thomson, Bloom's, and Cockayne's syndromes is thought to be autosomal recessive and this does not seem to apply in this family.

There are several diseases associated with membranoproliferative glomerulonephritis, but hitherto skin lesions as described here have not been among them. Although similarities exist between our patients and the sibship described by Mampaso *et al* with mesangial proliferative glomerulonephritis, diffuse glomerular deposits of IgM and C3, Rothmund-Thomson syndrome, and Clq deficiency the syndromes seem to be distinct.[4] Membranoproliferative glomerulonephritis has been recorded in siblings[5] but the only previous report that clearly shows that it can be a genetically determined disease was by Stutchfield *et al* [6] The disorder that they described was X linked without a skin rash and obviously distinguishable from that seen in our family, although it also had a normal complement profile.

Because the father's only renal biopsy specimen showed end stage renal disease it is impossible to be certain that the father's renal disease is identical with that of his son, but it would not seem an unreasonable assumption that it is. The progressive nature of the father's condition prompted us to consider trying to modify the progression of the child's glomerulonephritis. In view of his stable renal function, however, he is currently not receiving treatment

The autosomal dominant inheritance of this condition implies that there is a one in two risk of the offspring of this boy being affected. At present no means of definite prenatal diagnosis is available. Even if it were, it would probably offer little advantage in view of the slow progression of the renal disease into adult life, and the possibility of treatment by renal transplantation.

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# Karaya gum electrocardiographic electrodes for preterm infants

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SUMMARY Changes in transepidermal water loss were used to measure skin damage caused by removal of electrocardiograph electrodes in 20 preterm infants. Electrodes secured by conventional adhesive damaged the skin, leading to a potentially dangerous increase in skin permeability. In contrast, those secured by karaya gum caused no skin damage.

The preterm infant's skin is seen as a convenient site for the application of monitoring probes during intensive care. When the probes are removed, however, the adhesive strips off the superficial layers of the stratum corneum causing discomfort to the infant and weakening the epidermal barrier[1-3]; electrodes used for electrocardiography are the biggest culprits. Electrocardiographic monitoring of the preterm infant is almost universal, the electrodes are much larger than other surface monitoring devices and they are the most difficult to remove. A new karaya gum electrode has been introduced for neonatal use, and early experience suggested that it caused less epidermal stripping than an electrocardiograph electrode with conventional adhesive. This study was devised to compare the skin damage caused by the two types of electrode.

## Subjects and methods

Twenty preterm infants were studied. Their gestation ranged from 24 to 32 weeks (mean 29·7), birth weight 680 to 3020 g (mean 1500), and age from 1 to 10 days. An electrode with conventional adhesive (40426A Hewlett-Packard, United States) and one with karaya gum as the adhesive (Arbo-Pink H82V, West Germany) were fixed to opposite sides of the upper chest on undamaged skin. After 24 hours the electrodes were removed and skin damage assessed by measurement of transepidermal water loss with an evaporimeter (Ep 1, Servomed, Sweden) as previously described.[4] The water loss was measured at the electrode site and at an adjacent untouched area of skin 10 minutes, four hours, 24 hours and, where possible, 48 hours after removal. Reaction of the infant to removal of the electrode and appearance of the skin were recorded. The study was approved by the hospital ethical committee and informed parental consent was obtained. Statistical analysis was by Wilcoxon's matched pairs signed rank test.

## Results

Transepidermal water loss from the site of the conventional electrode was significantly higher than from adjacent skin with a mean of 83% higher at 10 minutes after removal and 32% higher at 48 hours (figure). By contrast, water loss from the site of the karaya gum electrode was not significantly different. When transepidermal water losses from the two electrode sites were compared, values from the conventional electrode site were higher than from the karaya gum electrode site on 63 of the 66 occasions that paired measurements were made. Removal of the conventional electrode was difficult and always painful and left an erythematous mark that lasted for several hours. The karaya gum electrode was easily and painlessly removed, and left no mark.

Both types of electrode gave good electrocardiographic traces. In two infants the karaya gum electrode fell off a total of four times (none of the conventional electrodes fell off), and on each occasion high ambient relative humidity (85%) was being used. In vitro studies showed that the karaya gum tended to soften when the relative humidity exceeded 70% and started to disintegrate above 90%.

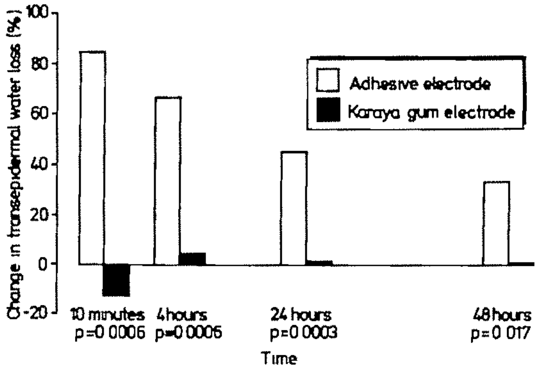

Figure *Transepidermal water loss from the site of removal of electrocardiogram electrodes*

## Discussion

The marked and persistent rise in transepidermal water loss from the site of the conventional adhesive electrode indicated substantial damage caused by stripping of the epidermis.[2] This explains why removal of the electrode was difficult and painful. In contrast, karaya gum stuck to the skin but did not strip the epidermis when removed, a property which makes it useful as a means of fixing a bag to an abdominal stoma. The thin skin of preterm infants is particularly vulnerable to trauma, as it lacks a well defined keratinised stratum corneum.[5] Its already poor barrier properties are considerably weakened when the outermost layers of the epidermis are stripped off, which result in higher skin water loss and an increased permeability to potentially toxic drugs and chemicals.[1] In addition, the damaged skin may be a site of entry for bacteria and result in local or systemic infection.[1] It has previously been shown that the skin under the adhesive ring of transcutaneous oxygen electrodes is protected by the prior application of a spray on plastic dressing (Op-site).[6] A further reduction in skin damage would result if karaya gum electrodes replaced conventional adhesive electrodes for electrocardiographic monitoring in preterm infants. They are three quarters the size of the conventional electrode used in this study (area of adhesion 6·5 cm$^2$ *v* 8·5 cm$^2$) and half the cost.

After removal the karaya gum electrode remains sticky and can easily be resited. This is a valuable property that allows for convenient repositioning of the electrode during procedures such as chest transillumination, chest radiography, and the insertion of chest drains. Monitoring of heart rate was satisfactory with both electrodes, and the only problem encountered was reduced adhesion of the karaya gum electrode at high humidity. This was a minor inconvenience that led to a loss of the electrocardiographic trace on only four occasions in 480 hours of monitoring.

We conclude that conventional adhesive electrodes damage the preterm infant's skin and recommend that the more convenient karaya gum electrode is used instead for electrocardiographic monitoring: babies prefer them.

We are grateful to Dr DA Curnock and Professor AD Milner for allowing us to study infants under their care We are indebted to the neonatal unit's nursing staff for their help and cooperation PHTC was supported by a grant from the Medical Research Council of Great Britain

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## *Personal view*

# Management of children with head injuries in district general hospitals

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Trauma is the major cause of death in children aged 1–14 years. A head injury may occur in isolation, but it is often just one component of a multiple injury. In these circumstances it is the head injury that is most likely to cause a fatal outcome.[1]

In the United Kingdom primary treatment of all patients with head injuries is traditionally carried out at district general hospitals with referral to neurosurgical units only in special circumstances. The reasons for this include the relative paucity of neurosurgical cover, the often isolated nature of the neurosurgical units, and the small percentage of patients with head injuries who require operations. The dangers of such a system for both adult and paediatric patients are obvious: it is non-neurosurgeons who make the primary decisions about neurosurgical referral, and neurosurgical junior staff are not unknown for their zeal in preserving their specialist beds for aneurysms and meningiomas, for example, especially when many of the injuries referred to them may not need specialist care. Much of the responsibility for this system must lie with the neurosurgeons, and it is only within the past few years that they have produced their own guidelines for the care of adults with head injuries.[2]

It is convenient to consider the management of children with head injuries in a district general hospital under the following headings: diagnosis, investigations, admission policy, treatment, referral to a neurosurgical unit, and follow up at the district general hospital.

### Diagnosis

The diagnosis of head injury, particularly in infancy, is overshadowed by the question of non-accidental injury. The problem has two aspects: is the child with neurosurgical problems suffering from a head injury at all and if so how has it been caused?[3] Brisk shaking of a young child will create damage that ranges from cerebral irritation (presumably due to blood over the surface of the brain) to cerebral oedema with or without subdural effusions. In these circumstances the intracranial pressure may be raised with fullness of the fontanelle and an increased head circumference, splaying of cranial sutures, and papilloedema and fundal haemorrhages. Chronic bilateral subdural effusions with raised intracranial pressure in a child under 1 year of age are almost always due to non-accidental injury, although there may be little external evidence of damage to the head. Even in older children non-accidental injury should always be suspected when the circumstances surrounding the trauma do not ring true.

### Investigations

Any child in whom an injury to the head is suspected should have a skull *x*-ray picture taken. Although this policy is sometimes derided by radiologists, from a statistical point of view a skull fracture (or splayed sutures) is a definite indication of the presence of an intracranial haematoma,[5 6] although its predictive power is not as great as in adults.[7] Where facilities for computed tomography are available any child presenting with a combination of a skull fracture and a disorder of consciousness lasting more than five hours after the injury should be scanned, particularly if the level of consciousness is low. A further indication is in the diagnosis of non-accidental injury. Blood over the cerebral hemispheres and along the falx in an infant with a story indicating a possibility of non-accidental injury is usually diagnostic,[8] and computed tomography has an important part to play in providing circumstantial evidence for the diagnosis.

### Admission policy

Admissions fall into two groups: those patients who obviously require hospital treatment because of the extent of their injuries are those who might be well enough to return home but in whom there is sufficient risk of complications for them to be kept under observation until the danger is over. Children suspected of having suffered non-accidental injury come into the first category and should always be admitted.

From the toddler age group upwards (and this is effectively from the time of suture closure) the indications for admission and for observation are the same. The incidence of raised intracranial pressure with or without an actual haematoma is highest among those whose skull *x*-ray pictures show a fracture and those whose level of consciousness had not returned completely to normal before they were seen in the casualty department. Children in either group should be admitted for observation for 24 hours. Obviously the time after the injury that the patient is seen in the casualty department will vary. Should a child seen within one hour who is still drowsy at that time but completely well two hours later be observed for the same time as a child seen three hours after the injury who is already fully recovered, regardless of the amount of time for which they were unwell? There is some evidence to suggest that any child who is the slightest bit unwell should be observed in hospital until five hours have elapsed from the time of injury.[illegible] If at that time they are perfectly fit and their skull *x*-ray pictures have shown no abnormality they could be allowed to return home providing responsible supervision is available. Children who remain unwell after five hours would then go through the full 24 hours of observation.

In infancy circumstances are a little different. It is in this age group that the highest incidence of intracranial haematoma occurs due to the presence of subdural collections.[9] Obviously an open anterior fontanelle allows some assessment of the intracranial pressure to be made. The incidence of non-accidental injury in this age group is also highest; therefore, although an assessment of consciousness cannot be carried out in the same way as for an older child, the same period of precautionary observation should be recommended. If the child appears at all unwell (and this includes a suspicion of raised intracranial pressure) when five hours have elapsed from the time of the injury then admission for observation should be mandatory. A skull fracture is also an indication for admission. A coma scoring and outcome scale for head injury in infants and toddlers has been suggested by Raimondi and Hirschauer.[9]

Observation in hospital is useless unless the nursing and medical staff are carefully instructed in the tests to be used and the action to be taken should the results change. The reason, apart from the obvious economic one, for trying to reduce the number of patients admitted to hospital for observation is to ensure that only those most likely to suffer a complication are admitted, and therefore the observations should be carried out in a more alert and suspicious fashion. Who should have responsibility for both the medical care and the observation of the child admitted after a head injury? There is no doubt that all such children should be in paediatric wards, and it is my view that the primary responsibility for them is best taken by paediatricians. I cannot see the point of the duty general surgical or orthopaedic team having to provide this extra care among all their other duties, and their experience in assessing sick children is likely to be limited.

## Treatment

Many children with head injuries show great irritability, but sedation may interfere with adequate monitoring of the vital signs and level of consciousness. Extreme irritability particularly in an infant may, however, warrant the judicious use of small doses of phenobarbitone.

Epileptic attacks in the first few hours after an acute head injury are common in children. Although they point to the possibility of the development of late post-traumatic epilepsy, these earlier seizures are likely to be indicative of a poor overall outcome only in children under 12 months old.[9] In older children they may occur after quite trivial accidents and in the absence of other neurological signs do not affect the statistical chances that the patient is harbouring an intracranial haematoma.

It is difficult to say when raised intracranial pressure ceases to be a normal part of a head injury and becomes a complication. There is no doubt that any child in whom raised intracranial pressure is suspected should have computed tomography. When this is not possible locally urgent referral to a neurosurgical centre should be sought. In infants the most likely site for an intracranial collection is the subdural space, and many paediatricians would recommend needle exploration in the first instance to aspirate any fluid.

Some children respond to even a comparatively trivial head injury by a delayed deterioration of consciousness without the formation of haematomas.[10] The aetiology of this strange condition is unknown but is thought to be associated with diffuse brain swelling associated with a generalised hyperaemia of the brain. It is best treated (as is the diffuse brain swelling of childhood that may follow a more severe injury) by intubation and hyperventilation, together with other methods of reducing intracranial pressure such as the administration of mannitol. Many paediatric units, whether in hospitals containing a neurosurgical department or not, are already accustomed to monitoring intracranial pressure as part of the management of encephalopathies and Reye's syndrome, and this facility has rationalised the measures for reducing intracranial pressure in children with head injuries.

## Referral to a neurosurgical unit

There are two categories of patient who require referral. The first comprises those whose primary injury has been sufficiently severe to make the paediatricians at the district general hospital reluctant to undertake their management; the number who fall into this category will depend on the local availability of computed tomography. A paediatrician faced with a sick child and no computed tomography is more likely to ask for neurosurgical help than one who knows from his own scans that he or she is not overlooking an intracranial haematoma. Although neurosurgical units may not be able to take all the patients that paediatricians wish merely for primary care and observation, there is no excuse for failing to discuss such a patient with the regional centre. Unfortunately, as mentioned above, the service provided for paediatric patients by a neurosurgical unit may be worse from the paediatric point of view than the one the child is leaving in the district general hospital. This is another reason why paediatricians may wish to keep such children under their own management rather than transfer them to a unit where they may be looked after by non-paediatricians in the corner of an adult ward. When the neurosurgical unit is within a large hospital the responsibility for the child should be shared between the two disciplines. Where neurosurgical units are isolated from any form of paediatric cover then referrals are likely to be fewer because the care they can offer is not as good.

The other category of referral to the neurosurgical unit comprises those children in whom complications have occurred during the period of observation. A deteriorating level of consciousness, changes in pupillary responses, and abnormalities of respiration or other signs of a rise in intracranial pressure even when this cannot be assessed by palpation of a fontanelle should always lead to urgent referral. If deterioration is rapid mannitol should immediately be given intravenously. The child's respiratory state at such times is always precarious, and serious consideration should be given to intubation and ventilation before an ambulance journey. If there is any doubt an anaesthetist should accompany the child. Once a decision to refer has been made it is best not to delay matters while trying to organise computed tomography locally when this has previously not been done. The neurosurgical unit is more likely to be able to arrange the scan at short notice because of the number of emergency scans it is accustomed to doing.

Is there any place for emergency surgery at a district general hospital? In my opinion there is no substitute for the prediction and then early recognition of complications followed by a prompt transfer to neurosurgeons. The problems posed by a patient with a severe head injury in the casualty department have recently been well described in an editorial that applies equally well to children and ends with these words: 'The essence of managing this type of emergency is not to panic but rather to consider and correct all extracranial abnormalities. The aim should be to present the neurosurgeon with a damaged but well oxygenated and well perfused brain. This will give the patient the greatest chance of recovery.'[11]

## Follow up at the district general hospital

A child with a head injury, particularly if old enough to be at school, may show a distressing but characteristic pattern of psychomotor problems because of the injury, and the paediatrician is undoubtedly the best person to supervise further management. Although individual symptoms and signs may appear vague, there is a well recognised constellation of reduced attention span and short term memory, irritability, emotional lability, and impairment of judgment that may follow any period of concussion. All these can interfere with the child's schooling and produce family interactions that add to the psychological difficulties, and yet they may not at first be recognised as being directly related to the child's disabilities. The paediatricians at the district general hospital may not have been directly concerned in any neurosurgical procedures, but with their understanding of the family background they are undoubtedly the best people to guide the patient and his or her family through these under recognised problems.[12]

What changes should be recommended in order to improve the care of children with head injuries in the United Kingdom? In district general hospitals children with head injuries should be admitted only to units that have adequate paediatric staff. Such a hospital should have the facility for computed tomography in order to reduce the number of children who are referred to neurosurgical units for care alone. Speedier organisation of transport from hospital to hospital for emergencies is also required, and the regional neurosurgical units themselves need modifying. Although at present there seems no possibility of funding specialist paediatric neurosurgeons, no regional centre should be without one neurosurgeon who is prepared to take particular responsibility for paediatric cases. In addition, neurosurgical units receiving children with head injuries should have paediatric wards and paediatric cover in the same hospital for their admission and care.

The problems posed by children with head injuries, particularly those who are very young, are difficult and carry heavy emotional overtones. Only by altering or adapting existing facilities in the ways described above will these young patients be able to receive the standards of care that they need.

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## *Current topic*

# Progress in adoption

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Adoption practice has changed during the past few years, partly because of changes in the law which followed the recommendations of the Houghton Stockdale committee in 1972. These gained statutory expression in the Children Act 1975, and various regulations under the Act have been implemented fairly recently. This paper is a review of the changes.

### Provision of an adoption service

There has been a fundamental shift from an emphasis on matching the needs of illegitimate babies and infertile couples to a perception of adoption as an essential component of a wide range of child care facilities. One of the changes, not yet legally enforced but taking place in practice, is the establishment of an adoption service in each local authority area. At present it may be provided either by local authority social service departments or by voluntary, non-profit making societies approved by the Secretary of State

The legal requirement to provide an adoption service has been accompanied by restrictions on private placements for adoption. Unless the proposed adopter is a relative of the child, nobody can lawfully enter into any agreement or arrange to facilitate placement of a child with a view to adoption. Likewise it is an offence to receive an unrelated child with a view to adoption except through a statutory or approved agency. This is intended to prevent abuse and ill considered placements, but it is not entirely watertight because private foster parents are permitted to seek an adoption order after a child has been with them for 12 months.

The Adoption Agencies Regulations (1983) set out various duties of agencies including a requirement that they must establish at least one adoption panel. Panels have medical advisers who are usually either paediatricians or senior clinical medical officers. Their duties include obtaining medical reports, evaluating them, and advising the agency Regulations govern confidentiality, disclosure, and transfer of records, and require that they are kept in a secure place for 75 years.

Regulations (the Adoption Agencies Regulations, schedule 3, rule 15 (4)) also define the content of reports on the health of the child and of the applicants; greater detail is required than in the past. The child's report has to include a health history of each natural parent (so far as is possible), a neonatal report, and a full health history and examination including a developmental assessment. Reports on applicants must include a family health history, marital history including (if applicable) the reasons for infertility, medical and obstetric history, a full medical examination, and details of consumption of alcohol, tobacco, and habit forming drugs.

### Applications to adopt

The age qualification for adopters has changed slightly in that applications may now be made by people who are at least 21 years old. A sole applicant must not be married, or if married the court has to be satisfied that the spouse cannot be found, or is separated and the separation is likely to be permanent, or is incapable of applying because of ill health. The law does not now prevent adoption by unrelated, unmarried, male applicants nor the adoption of female children by sole male applicants.

When an application for a hearing is filed, a reporting officer is appointed by the court. His or her duty is to ensure that the agreement of both parents in the case of a legitimate child, or of the mother in the case of an illegitimate child, is freely and unconditionally given. Signatures are witnessed and circumstances relevant to the agreement are investigated. A confidential report to the court is then provided.

Panels of guardians ad litem and reporting officers have been formed by regulation, and usually comprise experienced social workers and probation officers. They have to take an independent view and are not assigned to cases in which they have been involved with arrangements for adoption, nor to cases in which their employing authority has an interest.

There is still a trial period before an adoption order can be made. When an applicant is a parent, step-parent, or relative, or when placement has been by an adoption agency or pursuant of a High Court order, the child has to have his home with the applicants, or one of them, continuously for 13 weeks. Residence before an infant is 6 weeks old does not count and the earliest age at which an order can be made is therefore 19 weeks, as in the past. For all other cases, however the child must now have had his home with the applicants, or one of them, continuously during the preceding 12 months. If placement was not by an adoption agency, the applicants have to give at least three months' written notice to the local authority of their intention to apply for an adoption order. When an application is made the child becomes a 'protected child' and the local authority must arrange for him to be visited periodically to satisfy themselves about his well-being and to advise about his care.

## Parental agreement

There have been several changes in relation to parental agreement to adoption. It must be given freely, with full understanding and unconditionally. The parent cannot now (as formerly) make her agreement conditional on a particular religious upbringing, although the agency must have regard to her wishes. She may give verbal agreement at the hearing but it is more usual to present a written agreement that has been signed and witnessed. It may be withdrawn at any time before the order is made. The agreement of a putative father of an illegitimate child is not required unless he has been made a guardian of the child.

A new procedure allows agreement to be given or dispensed with at an early stage in the adoption process. It is called 'freeing' for adoption, and since 1984 adoption agencies have been able to apply to the courts for a 'freeing order' if at least one parent agrees to the adoption, or if the child is in care of the local authority and an application is being made to dispense with parental agreement. The effect of a 'freeing order' is that the rights and duties of the parent(s) cease and are taken over by the local authority of an approved adoption agency. Parental rights remain with the local authority or agency until an adoption order is made or the freeing order is revoked. Revocation is likely to be uncommon because a birth parent can only apply for it after 12 months if an adoption order has not been made, or the child is not living with parents with whom he has been placed for adoption. The attraction of the freeing procedure is that it reduces the period of uncertainty for all parties. Adoptive parents often become anxious before an order is made and in difficult cases this can be damaging because they may not commit themselves totally to the child.

## Dispensing with agreement

The statute with respect to dispensing with agreement has not changed, and the requirements are essentially the same as in the Adoption Act of 1958. They are that the parent(s) cannot be found or are incapable of giving consent, are withholding consent unreasonably, have persistently failed to discharge the duties of a parent without reasonable cause, have abandoned or neglected the child, have persistently ill-treated him, or have seriously ill-treated him, and there is no likelihood of rehabilitation.

There has been a good deal of case law, particularly in connection with the clause 'withholding consent unreasonably'. It was easily forseeable that there would be considerable legal argument about what is or is not reasonable. In the germinal case it was stated that welfare of the child must be taken into account because 'a reasonable mother surely gives great weight to what is better for the child'.[1] The view that welfare is of great importance was approved as authoritative in a House of Lords' judgment,[2] and since that time courts have, in varying degrees, subjugated other considerations to that of the child's welfare. Health and development is objective evidence of welfare and may therefore be important, as it is in wardship proceedings when welfare is the paramount consideration.

In adoption cases the child's interests are not quite paramount but courts do take serious account of the effect of moving him or her from a foster home in which he or she is settled. Time begins to run out on a mother whose child is placed with foster parents with a view to adoption, and a late change of mind was regarded as unreasonable.[3] Vacillation may also be taken into account.[4] On the other hand, it is the capacity of the parent at the time of the hearing rather than her history that is important,[5] and a reasonable parent is entitled to consider not only the welfare of the child but other factors such as her own wishes and welfare, the welfare of other children, and the wishes and welfare of grandparents.[6]

## Custodianship

This is a new type of order that has been available since December 1985. It differs from an adoption order in that it maintains legal ties between biological parents and their child and it may be revoked or varied. Unlike adopters, custodians (unless they are guardians of the child) are not allowed to arrange for his emigration from the United Kingdom, administer his property, change his name or religion, or agree to his adoption. Biological parents cannot apply for custodianship but it may be sought by any other first degree relative or step-parent or (in the case of illegitimate children) by those who would have been paternal first degree relatives had the child been legitimate. The person having legal custody has to agree, and the child has to have lived with them for three months. Unrelated people may apply with the agreement of the present legal custodian if the child has lived with them for a total of 12 months (including three months continuously) before the order. Anybody may apply without the consent of the custodian if the child has lived with them for three years.

The attractions of custodianship are that it gives legal security to step-parents or other relatives who look after children without facilitating dishonest relationships within families. It may also be used to make long term foster placements secure without severing links with biological parents. It has been recommended that custodianship should be used rather than adoption proceedings in long term fostering cases, unless the case for dispensing with parental agreement is strong.[7] The problem with custodianship is that it might give rise to future litigation and cause recurrent uncertainty for the child and his foster parents.

## Access to birth records

Adoption orders are generally final and their effect is that children are treated in law as if they had been born to the adopters. Some adopted persons wish to know about their biological parents and to have access to their birth records. In Scotland this has always been possible, but it has been available only since 1975 in England and Wales. The Registrar General is obliged to supply a copy of their birth record to any adopted person over 18 years of age provided that, if the adoption took place before 1975, the person has attended an interview with a counsellor. For adoptions after 1975 counselling is optional; it is available either at the Registrar General's office or at the relevant offices of the social services departments or adoption agencies.

Adoption has changed remarkably since the days when it was predominantly concerned with infant adoption by strangers and intrafamilial adoption. There are now about 2000 adoption orders annually that are made in respect of children in the care of local authorities who are often deprived and difficult, and the adoption of severely handicapped children is common. Legal practice has adapted to the changes, and the Law Commission (which is at present engaged in a reivew of child care law) will no doubt recommend further legislation.

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[5] Re H and Re W *Family Law Reports* 1983,**4**:614
[6] Re EL-G (minors). *Family Law Reports* 1983,**4**:589
[7] Re M (minors) *Adoption and Fostering* 1985,**9**:58

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# Referees and staff 1986–87

### Our referees

Submitted manuscripts are initially seen by the Editors who then send them to one or two expert referees for assessment. We thank the following people who kindly reviewed papers for our Journal in 1986 and 1987. Their expertise and the time so generously given has been a major factor in maintaining high standards.

*Referees in 1986–7*

Addison M
Addy DP
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Bamford FN
Bannister C
Barltrop D
Barnes ND
Barratt TM
Barrie H
Barson AJ
Baum DJ
Berg I
Bernstein J
Bewley B
Bissenden JG
Booth IW
Boyd RHB
Brande L Van Den
Brenner MK
Brocklebank T
Brook CGD
Brownbridge G
Buckler JMH
Campbell AGM
Carpenter RG
Carswell F
Cartwright S
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Clayden GS
Cockburn F
Cohen AT
Congdon P
Conway S
Cooke RWI
Coulter JBS
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Craft AW
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Davies DP
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Dinwiddie R
Dodge J
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Houston IB
Hughes H
Hughes IA
Hull D
Hunt L
Hunter AS
Illingworth CM
Illingworth RS
Irving HC
Isaacs D
Janossy G
Johnston DI
Jones DM
Keeling J
Kelleher J
Kennedy C
Kiely EM
Kilby AM
Kinmonth AL
Klenerman L
Kovar I
Kuzemko J
Lake BD
Larson HE
Larcher V
Lask BD
Lenney W
Leonard JV
Letsky EA
Levene M
Levick RK
Levinsky RJ
Lewis I
Lilleyman JS
Lissauer T
Littlewood JM
Lloyd D
Lloyd JK
Longson M
Louvois J de
Lucas A
Lynch MA
Macartney FJ
Macfarlane JA
MacFaul R
MacLaurin J
McClure BG
McElwain TJ
McIntosh NM
McKenzie S
McKinlay IA
McNeish AS
Mann J
Martin J
Matthew DI
Mearns M
Meire H
Milla PJ
Milner V
Milner AD
Milner RDG
Morley DC
Morris Jones PH
Mott MG
Mowat AP

Moxon ER
Mucklow ES
Mugford M
Nelson R
Neville BGR
Newcombe R
Newton RW
Nicoll AR
Noah N
Oppé TE
Orme RC L'e
Parkin JM
Patel R
Payne B
Pearson SB
Peckham C
Pembrey ME
Peto J
Pharoah P
Pippard MJ
Polnay L
Pope M
Poskitt EME
Postlethwaite RJ
Preston N
Price DA
Price JF
Pritchard J
Proesmans W
Puntis J
Radford M
Rayner PHW
Reeves J
Richman N
Richmond S
Rigby ML
Rivers RPA
Roberton NRC
Robinson MJ
Robinson RJ
Robinson RO
Robson WJ
Rolles CJ
Rosenbloom L
Rutter N
Rylance GW
Sardharwalla IB
Sands J
Savage MO
Shalet SM
Shaw DG
Shaw JCL
Shinebourne EA
Sibert JR
Sibley Y
Silverman ML
Simpson HRP
Skuse DH
Smellie J
Smith CS
Smith H
Smith I
Smith SEW
Smithells RW
Van Someren V
D'Souza SW
Speidel BD
Speight N
Spitz L
Stacey TE
Stanton AN
Stephenson JBP
Stern CMM
Stewart AL
Stewart AM
Stimmler L
Stores G
Strang LB
Strobel S
Super M
Tanner MS
Tarlow MJ
Taylor D
Taylor DC
Taylor E
Taylor IG
Taylor JFN
Tripp JH
Trompeter RS
Turner TL
Tynan MJ
Tyrrell DAJ
Verbov J
Verrier-Jones K
Volans G
Wales JKH
Walker V
Walker-Smith JA
Wall RA
Ward J
Warner JO
Watson JG
Watts R
Webster ADB
Webster D
Weindling AM
Weller PH
Wensley RT
Wharton BA
White RHR
Whitehead RG
Whitelaw A
Wigglesworth JS
Wilkinson AR
Wilkinson JL
Winter R
Winterborn MH
Wood CBS
Wright M
Wright V
Wynne JM
Young I
Zuckerman AJ

## Staff

Several changes in staff have occurred in the past year. Roy Meadow completed his term of office as Editor and Malcolm Chiswick became a Co-Editor. David Milner, Richard Robinson, and Brian Wharton were appointed Associate Editors.

Jeremy Weightman, our Technical Editor, resigned to become Editor of a computer journal in February. We thank him for his meticulous work. At short notice, Caroline White, who is also Technical Editor of the *Journal of Clinical Pathology*, agreed to steer the Journal through this difficult year with the help of Mary Evans. We are grateful to both of them for their strenuous and successful efforts to edit and publish the Journal on time with a full complement of pages despite many obstacles. We welcome Susan Heels as our new Technical Editor, and she will be assisted by Mary Evans. Helen Raynes, who was responsible for the extremely efficient running of the "Archives" office, has started a course of further education, and we welcome Janine Oesi, who has taken her place.

THE EDITORS

*Archives of Disease in Childhood,* 1987, **62,** 1292–1293

# Correspondence

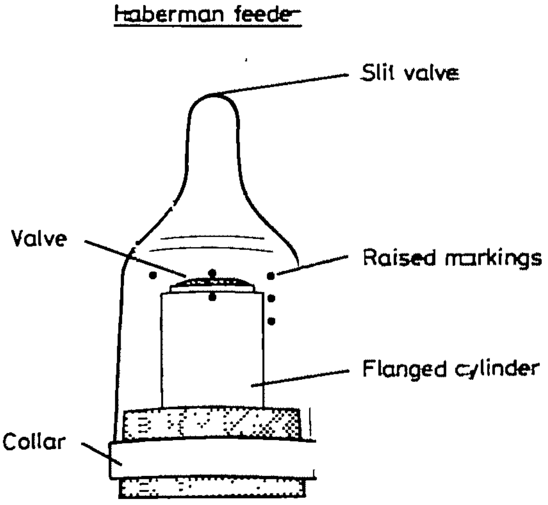
## New feeder for infants with cleft palate

Sir,

Early feeding difficulties in infants with a cleft palate are well documented[1] as is poor mother-infant bonding.[2] For many years these infants have been fed with various makeshift modifications of a teat. Over the last year we have been using a new feeder specifically designed to overcome many of the problems of feeding such infants.

The new 'Haberman' feeder consists of four components (see figure). The flanged cylinder (solid, food grade silicone) has one end formed to accept a mushroom valve through which the milk enters the teat; this provides a non-return passage for milk from a conventional feeding bottle. A lateral channel is incorporated in the posterior aspect of the flange to allow air to enter the bottle, preventing a vacuum being formed in it. The teat is made from tear resistant food grade silicone. It is soft, malleable, and transparent and fits over the cylinder to form a liquid and airtight seal. The mouthpiece has a slit valve opening with markings on the teat body to indicate the position of the slit opening relative to the infant's mouth; this controls the flow of milk to the infant's mouth. Sucking by the infant compresses the teat alone so that it is not wasted on compressing air inside the bottle. The feeder is attached to the bottle by a collar.

We have recently used the new feeder with six infants: two had bilateral clefts and the remaining four had unilateral clefts. Their gestational ages ranged from 36 to 42 weeks with a mean weight of 2·8 kg (range 1·9 kg–3·2 kg). Three infants were initially fed with conventional teats while the remaining three used the Haberman feeder from birth. It was found that the infants fed faster and more easily with the new feeder. There was less aerography and consequently less vomiting. The weight gain was satisfactory throughout. The parents had no complaints while using the feeder and in those where a conventional teat was used first, the Haberman feeder was preferred.



We believe that the Haberman feeder is a significant advance in the feeding of infants with cleft palates and should be the preferred feeder rather than conventional means. A further long term study is underway.

The feeder is manufactured by Camberley Rubber Mouldings Ltd, Farnborough, Hampshire.

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## Radionuclide scans in reflux nephropathy

Sir,

The excellent article by Professor White on the management of urinary tract infection mentions radionuclide scans only briefly.[1] A technetium dimercaptosuccinate (DMSA) scan is an indispensible tool in the assessment of reflux nephropathy.[2] Ultrasound has an advantage over the intravenous urogram (IVU) in a young child because the kidneys are accessible to a high frequency high resolution transducer and the delineation of renal anatomy is usually better than on an IVU with poor contrast excretion and interfering bowel gas shadows. Certainly in children under the age of 3 years ultrasound should be the first investigation, followed by a DMSA scan as the second investigation, once an obstruction has been excluded.

In a consecutive series of 25 infants studied by DMSA scans within three weeks of their first febrile urinary tract infection, 15 kidneys in 10 infants were found to have focal parenchymal defects suggestive of upper tract involvement.[3] Cystograms in these 10 infants subsequently showed ipsilateral reflux to 10 of the abnormal kidneys, five kidneys were drained by non-refluxing ureters and no contralateral reflux was observed to kidneys which were normal on DMSA scanning. These observations have subsequently been extended and we have found that the DMSA scan exceeds both the IVU and ultrasound in its ability to detect the kidney at risk from reflux nephropathy (publication in preparation). Merrick *et al* compared the

IVU and DMSA scan and found the DMSA scan more sensitive for detecting established pyelonephritis in older children.[4]

It is now my practice to arrange a DMSA scan before a cystogram in all children over 1 year of age. There is no doubt that a DMSA scan is less traumatic to the child (and the radiologist) than a cystogram and should therefore be placed earlier in the diagnostic sequence. An abnormal DMSA scan is an absolute indication to proceed to a cystogram as more than two thirds of the children will have reflux. If the DMSA scan is normal reflux will be a rare event and probably of little long term significance, but a careful prospective study would be required to establish this point. In the meantime, I would urge paediatricians to request DMSA scans from their radiologist colleagues who will probably be delighted to carry out these relatively non-invasive tests particularly if such a change in policy results in fewer cystograms in the toddler age group.

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## Corrections

### When not to do a lumbar puncture

In the annotation entitled 'When not to do a lumbar puncture' by DP Addy (*Arch Dis Child* 1987;**62:** 873–5) we apologise that the meaning of some sentences in the published version were not clear. The original version follows.

**Page 874. Second sentence of second paragraph:** Treatment including chloramphenicol will usually be adequate in meningitis caused by any of the usual three organisms.[11]

**Page 874. Final sentence of left-hand column:** Whilst it may be wise to remove only a small amount of CSF when diagnostic lumbar puncture is performed, 'careful' lumbar puncture is not the answer since CSF leak through the punctured meninges may persist after the procedure.

**Page 874. Third sentence of fourth paragraph:** Fundal signs of raised pressure are not to be relied upon but evidence of incipient coning would make lumbar puncture a foolhardy procedure.

**Page 875. Penultimate paragraph:** I shall consider treatment without lumbar puncture: when the diagnosis of meningitis seems clear and the child is very ill, **or** has a typical purpuric rash, **or** there is fundoscopic evidence of raised pressure, **or** there is impairment of consciousness, **or** there are other signs of incipient coning, **or** the child has been ill for several days.

### Acarboxyprothrombin activity after oral prophylactic vitamin K

In the paper 'Acarboxyprothrombin activity after oral prophylactic vitamin K' by von Kries, Kreppel, Becker, Tangermann, and Gobel (*Arch Dis Child* 1987;**62:**938–40) we apologise that the word 'activity' should have been published as 'concentration' throughout the paper.

*Archives of Disease in Childhood*, 1987, **62**, 1294–1297

# Book reviews

**Cardiovascular Problems in Paediatric Critical Care.** Edited by David W Swedlow and Russell C Raphaely. Pp 311: £35·00 hardback. Churchill Livingstone 1986

The objective of this book is to give a comprehensive overview of current aspects of cardiovascular physiology as required by those concerned with paediatric intensive care and to deal in some detail with all aspects of investigation and management of cardiovascular problems as they present in the intensive care unit. This volume is clearly written from the point of view of specialist intensive therapists and is aimed chiefly at those who are training in that field of paediatric care. It would seem to be aimed largely at the American market and much of its content is heavily biased towards North American practice.

The general concept of this monograph is sound and might be expected to have wide appeal to paediatricians, paediatric surgeons, and paediatric anaesthetists who are concerned with intensive care, but in practice the book is unbalanced and probably of rather limited value to a high proportion of its potential readership. The initial section on cardiovascular physiology is lengthy and makes heavy reading, but it does include a wealth of information on most aspects of cardiovascular physiology and is very heavily referenced (more than 450 references for this chapter alone)

Two chapters on investigation follow the first of these (non-invasive tests) provides a detailed account of echocardiography as it relates to assessment of ventricular function and pulmonary artery pressure, radionuclide imaging, and Doppler assessment of cardiac output There is a brief mention of computed tomography and magnetic resonance imaging (currently of doubtful relevance in the intensive care unit environment). The chapter on invasive assessment discusses a variety of arterial and venous cannulation sites and methods plus details of pressure monitoring and cardiac output measurement by dye dilution, thermodilution, etc. Systemic and pulmonary resistance calculations are also discussed briefly. A further fairly large and heavily referenced chapter relates to anaesthetic considerations of cardiac patients and is aimed specifically at those involved in cardiac anaesthesia and post-operative care

The remaining one third of the book covers treatment. A chapter on 'preload manipulation' repeats a great deal of the information contained in the first chapter on cardiovascular physiology and actual discussion of treatment is limited to two pages A brief chapter dealing with 'afterload manipulation' largely comprises a series of dose regimes of different vasodilators Again the chapter on 'contractility' repeats much of the physiology and gives limited practical information about inotropic drugs (all with American names) The final two chapters on heart rate and rhythm and cardiopulmonary resuscitation are both of rather limited value. Arrhythmias are dealt with superficially and anti-arrhythmic drugs are limited to those currently available in the United States (neither amiodarone nor flecainide get a mention)

All in all this is a rather disappointing and unbalanced book that will not be of value as a manual on cardiovascular aspects of intensive care; the sections on cardiovascular physiology and non-invasive investigation, however, do contain much useful information and may prove a valuable source of reference. For this reason, and in view of the relatively low price by current standards, the book should find a place in the libraries of institutions with a paediatric intensive care unit Being orientated largely towards older children and infants (beyond the neonatal period), however, it is less likely that this volume will prove useful to those concerned specifically with neonatal intensive care.

J L WILKINSON

**Breasts, Bottles and Babies.** By Valerie Fildes. Pp. 462· £19·75 hardback. Edinburgh University Press, 1986

This is an excellent reference book and source material for anyone interested in the history of infant feeding and the folklore surrounding it. The main part of the book comprises the author's PhD thesis on infant feeding between 1500 and 1800—from the beginning of printed books to the end of the pre-industrial period Her review is world wide but concentrates principally on Europe and, of course, the United Kingdom. The significant changes in the relations between doctors, midwives, and the public on the views and advice given on infant feeding are well recorded At a time when paediatricians and midwives are promoting breast feeding it is a well to remember that it was sometime regarded as being only suitable for 'we nurses' and those of a lower station. The most remarkable pioneers in changing thi attitude were those upper class mother who were prepared to break this convention and work at the foundling hospital in this country The first part of the book shows some signs of having been added on in order to make the book more comprehensive Nevertheless, the views of antiquity and the medieval period towards infan feeding are elegantly expressed

Throughout the book there are excellent references and reproductions in black and white of pictures and line drawings of original feeding vessels and paintings al concerned with infant feeding This could be sheer delight to the art historian, and would certainly complement the excellen collection that the late Ronald MacKeith assembled about the art of infant feeding It would be pleasing to think that such a text book was available at any district general hospital, however, the price and the somewhat epigrammatic title might put off a serious reader.

C H NOURSE

**Advances in Pediatric Infectious Diseases. Volume 2.** Editor in Chief S C Aronoff Pp 192 £21·50 hardback Year Book Medical Publishers, 1987

In this second volume of a series directed at general paediatricians the editors have chosen eight subjects of current interest for review The range is broad, but there is welcome coordination of several contributions The target of topicality is hit straight away in the first chapter. Protection of young children against invasive infections caused by *Haemophilus influenzae* type b (Hib) is a new public health goal, and immunisation regimes using various different modifications of capsular antigen are currently being used or considered for use in the United States and Europe In their chapter on the epidemiology and immunology of infections with Hib, Hetherington and Lepow provide the essential basis for evaluating such strategies.

With more and more use of nursery facilities for small children there is growing concern about a possible increase in serious infections, from Hib meningitis to hepatitis. The second chapter, Infections in Day-Care Centres, complements the epidemiological part of the first, and gives a useful summary of what we do and do not know about the risks involved and what can be done to minimise them

Two scholarly reviews—of antiviral treatment and of perinatal enteroviral infections—are followed by four articles taking a practical approach to the subjects they cover There are reviews of the management of pulmonary infections in the immunocompromised child, of childhood tuberculosis, and of urinary tract infections. This last, while usefully practical in microbiological matters and commendably free of dogma in discussion of the management of reflux, disappointingly omits any appraisal of different imaging techniques and their different indications in practice Finally, Sixby's chapter, Routine Immunisations and the Immunosuppressed Child, is a *tour de force* Extensively referenced, to 203 sources, this is a highly readable and very useful summary of important information for all those helping to care for these children

As part of an add-on series keeping infectious diseases in the forefront of paediatricians' minds, this collection well deserves the attention of the wide audience to whom it is addressed

J S KROLL

**Respiratory and Alimentary Tract Diseases.** Edited by H S Rosenberg and J Bernstein Pp 218· £100 hardback. Karger, 1987

Some books give the impression that they have been organised in the spirit of a dinner party whereby the conversation is a product of those who attend rather than the reason for their invitation This book is volume 11 in a series entitled *Perspectives in Pediatric Pathology*. It begins with a short tribute to that Edinburgh pioneer of the discipline Dr Agnes Macgregor by her successor Dr Douglas Bain, they are now both sadly deceased. The reviews that follow are of very diverse appeal. Dr Robertson gives a good account of the experimental background of neonatal surfactant deficiency and there is a comprehensive review by Dr Cutz on pulmonary haemosiderosis Dr Landing and his co-workers contribute two chapters The first is an account of the pulmonary lesions in 14 children with thalassaemia major that would more appropriately have been published in a journal The second has no pretensions to being a pathological treatise as it is devoted to the normal anatomy of the myenteric plexus as shown by flat mount preparations. There are two chapters related to the oesophagus. one on mucosal biopsies and the other on the pathophysiology of reflux and oesophagitis The book concludes with a review of Indian childhood cirrhosis and a form of megacolon indigenous to the African Bantu.

Paediatric pathology has become too large and complex a field for any kind of perspective to be gained into two organ systems in so slim a volume. The book lacks cohesion and the authors would have been far better selecting eight reviews on a more well defined area like the childhood liver, large intestine, or the neonatal lung It is a book best seen in the context of the series and as such is more an acquisition for the reference library than the individual.

A J BARSON

**Decision Making in Child Neurology.** By D W Dunn and L G Epstein Pp 217: £41 50 hardback. B C Decker Inc, 1987

The authors of this book state clearly in the preface that they see the work as a practical guide for the paediatrician who is dealing with a wide range of neurological problems; the aim is to give a guide to paediatric neurological thinking They also state that it should be useful for revision and in preparing lectures.

The book is part of a much larger series with a similar format, which comprises two pages for each subject. On the right hand page there is an algorithm to guide the reader through making a decision; on the opposite page is an expanded set of notes A variety of clinical problems are covered, specific diagnoses—for example, meningitis, presenting features—for example, acute ataxia, and practical problems—for example, brain death Some subjects lend themselves better than others to this format and often the algorithm does not add a great deal to the notes which are in general concise and well thought out, up to date and practical, though of necessity somewhat didactic

One might quibble with some aspects of drug treatment and recommendations, but I suppose the excessive use of phenobarbitone just reflects North American usage There is also a tendency to suggest investigation of neurological disease rather more extensively and earlier than we would in the United Kingdom

The book is up to date and well referenced It gives a practical, concise guide to the diagnosis and management of a wide range of subjects including most of the common problems in child neurology, and some that are less commonly seen by the average paediatrician—for example nystagmus or acute vascular problems It is not so much a book to read for an in depth assessment of a particular problem, but I consider it to be a useful book (not only for revising for exams and preparing for lectures as the authors suggest), but a practical guide which would be of more use on the wards than in the reference section of the library

S H GREEN

**Manual of Child Neurology.** Owen B Evans Pp 435: £32·50 paperback Churchill Livingstone, 1987.

The author states that this book is a manual and not a text book and that it is written for 'paediatricians and other physicians involved in the primary care of children.' The book is divided into eight sections with the first two being on neurological examination and neurodiagnostic procedures The following sections cover relevant groups of neurological disorders in childhood. Each chapter within a section has a short list of 'selected readings ' The illustrations are a combination of line drawings by the author and photographs that seem mainly to be of muscle biopsy specimens or computed tomograms There are a large number of tables most of which are designed to give the reader a very wide range of differential diagnoses in any one clinical situation

With at least a handful of good books on paediatric neurology now available it is difficult to see where this book will fit in and make a contribution. In many of the sections the author starts with very basic statements about the structure and function of the nervous system, but then goes on to give the reader extensive lists of differential diagnoses (some of which are a little questionable) but no guidance as to which disorders are common or which are rare The balance of space given to different disorders is very variable and many of the opinions expressed are hardly contemporary Indeed, in the 'selected readings' that accompany each chapter at least half are for publications that are more than 10 years old. While the author has written a book that is aimed at those in primary care, and may have been one of the first to do so, it is very difficult to see that this is going to truly enlighten Sadly I fear that it will only confuse

GWILYM P HOSKING

**Manual of Paediatric Emergencies.** Edited by J R Zanga. Pp 511: £32·00 paperback Churchill Livingstone, 1987.

The subjects in this book were selected from experience with the major presenting problems found in a busy city emergency paediatric unit in the United States. The sections on cardiopulmonary resuscitation, major medical, surgical, and traumatic emergencies, and child abuse are excellent. Common presenting symptoms for medical conditions, such as headache and abdominal pain, are barely mentioned The lack of information on minor injuries is also significant. At least 50% of children presenting to the urban accident and emergency departments in the United Kingdom have had minor trauma, but many important aspects in this area of work — for example, hand injuries and epiphyseal injuries — are not included in the clinical sections of the book.

The manual is valuable for the diagnosis and management of children presenting with major illness or injury, but has limited value as the 'ready reference book . . designed for the emergency department.' Several more comprehensive books already fulfil this role.

W J ROBSON

**Respiratory Disorders of Infants and Children.** Jan A Kuzemko. Pp 101: £14·50 paperback Castle House, 1987.

This book starts with useful revision chapters on the basic anatomy, embryology, and physiology of the respiratory tract. Of the remaining 13 chapters several are too brief to be very useful and are little more than lists. The chapter on symptoms and signs I found vaguely irritating: for example, the author says that the word 'stridor' causes confusion and should be abolished. but he fails to suggest an alternative and proceeds to continue to use the word himself

The chapter on upper respiratory tract infection is good; it is practical, detailed, and helpful especially the section on epiglottitis and viral 'croup'. Similarly, there is much that is good in the chapter on asthma, as one would expect from an author with a known special interest in the subject. It is disappointing, however, to see him perpetuate the teaching that only 2–5% of children have asthma rather than the 10–15% that is now generally accepted He lists seven possible investigations of varying degrees of complexity without any guidance as to how appropriate any of them would be in the every day clinical management of asthma.

This rather theoretical approach is a drawback for a book that purports to be aimed at the primary care physician. Similarly, any general practitioner reading this book would have a negative reaction on seeing immune deficiency, $\alpha_1$ antitrypsin deficiency and collagen diseases included in a list of 'Common causes of wheezing' Overall, I would regard this as very much a 'curate's egg' of a book. whether the reader is a medical student, general practitioner, or paediatrician.

A N P SPEIGHT

**Fetal and Neonatal Pathology.** Edited by Jean W Keeling Pp 590: £95 hardback. Springer-Verlag, 1987

After many years of drought we are now being presented with new books on children's pathology every few months, and I suspect that there is not a paediatric pathologist who is not writing a chapter for somebody's book at this moment! This book has one major author-editor with many others contributing chapters About half the book is on general topics such as perinatal autopsy, the placenta, and examination of the fetus; and the rest is on the pathologies of organs and systems The standards of the different sections varies greatly. The naked eye pictures are generally good but the microphotographs are very variable and often poor

The data presented is insufficient for a specialist pathologist and the whole is aimed at the general pathologist who deals with fetal and perinatal deaths It is insufficient to enable the general pathologist to deal with infantile diseases such as Hirschsprung's disease, but gives an indication of the procedures involved It would enable him to diagnose hyaline membranes but he would know less about the factors of their production or of effects of intensive care on the newborn lung than does the paediatric neonatologist. There is much internal cross referencing but for the non-specialist the index could have been made wider; thus the inclusion of 'congenital megacolon' or simply 'megacolon' would have helped in the finding of 'Hirschsprung's Disease'.

To say that a book is good in parts is not to label it a 'curate's egg ' This book gives the general pathologist a rapid and convenient insight into the pathologies of this age group It is recommended for inclusion in the libraries of general hospitals and of paediatric departments.

J L EMERY

**Pediatric and Adolescent Diabetes Mellitus.** S J Brink Pp 454· £34·00 paperback. Year Book Medical Publishers, 1987.

This book provides a comprehensive review of paediatric diabetic management from an American perspective. The editor and main author, Dr Brink, draws on wide experience gained in part as senior staff paediatrician at the Joslin Clinic and he combines a critical approach to clinical care with a strong awareness of psychological issues and a great respect for the children with diabetes and their families. In addition, data from the youth registry set up by Dr Brink and including clinical information on over 1000 young patients (aged 1–21 years) are used as a basis for the management policies advocated

The book is laid out in three sections: Part I is a practical manual of care; Part II covers new theories, treatments, and associated problems, and Part III discusses preventative medicine and counselling I found the middle section most successful; the contributions on epidemiology, genetics, and immunology provide a concise up to date summary and excellent advice is provided on the prevention and management of ketoacidosis and on sensible dietary guidelines The final section on preventative medicine and counselling draws on theories of normal child development to discuss methods of managing the psychosocial aspects of diabetes, much good sense here tends to get lost in the jargon

The section on practical management covers chapters for children under 5 years, 5–9 years, and the 10–21 year age groups separately. Each part is followed by a psychosocial commentary written by a psychologist or social worker. The sections are designed to be used independently and as a sult are highly repetitive. They cover le new ground, but the transatlantic erspective is interesting with its emphasis n outpatient care from diagnosis and the ssumption that a multidisciplinary team ill be available to offer home based ducational support

It would be a pity if either layout or rgon discouraged paediatricians from king advantage of Dr Brink's fine critical eview of the paediatric literature on diaetes and its humane clinical application It hould be available to the team in all aediatric diabetes outpatient departments

A-L KINMONTH

**rinciples of Pediatric Neurosurgery.** eries editor A J Raimondi **Head Injuries n the Newborn and Infant.** Edited by A J aimondi, M Choux, C Di Rocco Pp 292· M 118 hardback. Springer-Verlag, 1986

irst a welcome to a new series, *Principles f Pediatric Neurosurgery*, of which this olume is the first. In the United Kingdom e treatment of the head injured child is ss than ideal: there are no full time paeiatric neurosurgeons and some neurosurical units do not even have specialised acilities for the care of paediatric cases. et trauma (and particularly any cerebral omponent) is the commonest cause of eath in patients under 14 years of age and e are all well aware of the complexities of he child who has suffered a non-accidental njury.

If the principles of management for the lder child are not so very different to hose of the adult, the same can certainly ot be said for the newborn and infants ho are the subject of this book. That we ll survive the traumas of child birth pparently unscathed seems miraculous nough but how do subsequent injuries ffect a brain that is still involved in the ital processes of myelination and dendritic rborisation? The contributors to this book ome from all over the world and they deal n turn with such basic subjects as the intrauterine development of the skull, the effects on head form of intrauterine compression and passage through the birth canal, intraventricular haemorrhage and the epidemiology of craniocerebral trauma in the first two years of life before describing the more expected subjects of diagnosis, management, and outcome

With function and development in the infant brain so intimately mingled there must always be uncertainty and therefore concern about the effects of trauma Any book which reduces this atmosphere of mystery is to be welcomed, and therefore I have no hesitation in recommending this volume to all those concerned in the care of these unfortunate young patients.

R HAYWARD

**Complications of Paediatric Surgery.** James Lister. Pp 294 £29·50 hardback Baillière Tindall, 1986

The main purpose of this volume is to bring to the notice of the general surgeon, and particularly the surgeon in training, the complications that may follow quite simple procedures in children and to indicate how they may be avoided. This is the stated aim of the book The intention was to avoid the neonatal surgery that is undertaken in specialist units and the less common conditions of children.

The text is liberally illustrated and the numerous illustrations (clinical photographs, *x* ray films, and diagrams) are often useful for diagnosis Neonatal surgical conditions are given space — for example, four *x* ray pictures of infants with oesophageal atresia each showing a slightly different aspect. The interesting presentation of neonatal surgical problems is balanced by the common conditions such as inguinal herniae It seems a pity in discussing the complications that nothing more is said about strangulation than that it is rare in childhood The point that it is only likely to occur in the very young infant is not made, whereas incarceration can occur at any age. Conditions such as appendicitis, intussusception, and undescended testes are reviewed The book would seem to be of most value to paediatricians along with surgeons in training rather than to experienced general surgeons. For the former groups it gives a good oversight to many of the conditions requiring surgery in infancy and childhood

D G YOUNG

**Radiology of the Pediatric Chest.** Alvin H Felman Pp 484. £80·00 hardback McGraw-Hill, 1987.

In his preface the author indicates his intention to produce a book both for clinicians who wish to interpret chest radiographs and for radiologists who need to be aware of the clinical manifestations of disease. This approach is difficult and often fails in its objective, but this is a successful and useful book.

Sections deal with congenital abnormalities, neonatal pulmonary disorders, the mediastinum, roentgenographic patterns in pulmonary disease, infections, and infestations The final two sections deal with a miscellany of conditions including tumour and trauma and with the more recent techniques (by a coauthor) of computed tomography, magnetic resonance imaging, and ultrasound, although relatively little mention is made of the potential of nuclear medicine. The range of diseases covered is very wide. The text is adequately comprehensive in clinical, pathological, and radiological content. The numerous illustrations are generally good and the references profuse and pertinent.

For the paediatrician who wishes to acquaint himself with chest radiology this is a commendable book but the price, which is very high, many may feel prohibitive. The radiologist may well feel that his money is better spent contributing towards a modern edition of 'Caffey ' For those in training this is an educative and readable text which could usefully be available in departmental libraries.

D G SHAW

*Archives of Disease in Childhood,* 1987, **62,** 1298

***British paediatrics***

# Paediatric intensive care

A working party of the BPA has published a report on the facilities, organisation and staffing for intensive care of children outside the neonatal period. The working party identified 22 paediatric intensive care units in the United Kingdom. In almost all of them medical care and junior staff were provided by paediatricians. Of the consultants in overall charge with responsibility for ventilatory care, about half were anaesthetists and half were paediatricians. One third of an annual total of 4000 children admitted for intensive care were treated in general adult intensive care units, in many cases sharing open plan areas with adult patients. The bed requirement for paediatric intensive care was estimated to be one per 40 000 of the child population and the suggested ideal size of a paediatric intensive care unit was from eight to 10 beds with a minimum of five. One unit of parental accommodation should be provided within the hospital for each intensive care bed. The report includes a list of recommended equipment and supporting services for paediatric intensive care units.

The working party believes there should be a national network of at least one paediatric intensive care unit per region to treat the more complex cases and a regional network of general adult intensive care units with improved facilities for children to deal with the less complex case . In some of the larger paediatric departments it might be possible to provide intensive care in a children's high dependency area; in smaller departments a link with the neonatal intensive care unit might be preferred. One consultant should be on call for the unit at all times, and house officers, on a rota of at least one in three, should work full time on the unit for periods of at least three months. At present the mean number of nurses per bed is 3·5 whole time equivalents, which the working party considers to be inadequate.

Training was considered to be of particular importance. Medical training in paediatric intensive care should be included in general paediatric training and should also be part of the training for those specialising in intensive care for adults. Only 1·3% of nurses working in general adult intensive care units had received children's nursing training and there should be a greater emphasis on training for the staff of these units.

The working party recommends a further survey to determine more precisely the future requirements for paediatric intensive care.

A D M Jackson

# Paediatric training in the United Kingdom

British paediatrics has a long history of involvement in child health overseas, especially in the developing countries, and has always felt an obligation to help doctors from those countries who come to the United Kingdom for postgraduate training. Twenty years ago the British Paediatric Association (BPA) published the first edition of its booklet, *Paediatric Training in the United Kingdom*, as a guide to opportunities for postgraduate paediatric training in this country. The fourth edition of this booklet, which was published in January of this year, reflects the expansion in postgraduate medical education and the increasing complexity of the regulations concerning employment for overseas doctors.

This latest edition describes the British system of postgraduate training and offers general advice on preparing for a visit. It explains immigration requirements and the regulations for registration with the General Medical Council. There are detailed lists of the various paediatric courses available and the organisations that offer scholarships and fellowships. A helpful check list of the steps to be taken by prospective trainees refers to the relevant pages in the booklet. An appendix gives the addresses of the regional postgraduate deans, together with a map indicating the location of the university centres.

*Paediatric Training in the United Kingdom* was written for the BPA by its overseas committee and will undoubtedly fulfil the wish of the committee to strengthen the links between British Paediatrics and countries overseas.

A D M Jackson

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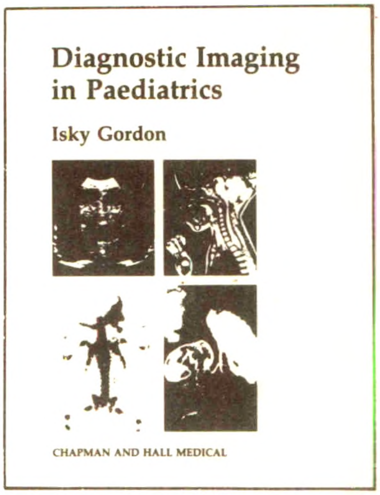

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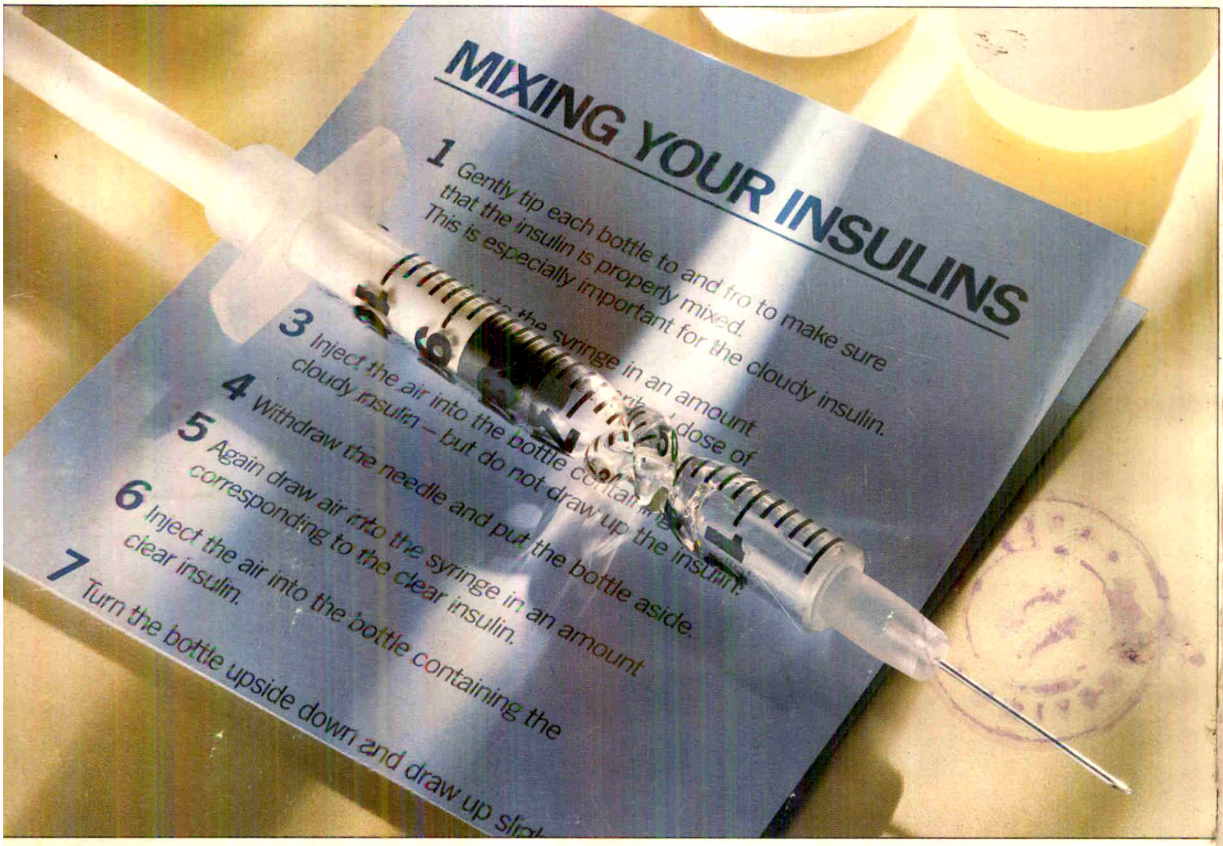

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*ecautions:* Patients transferring from other insulins may require a dosage ustment. Concomitant therapy with thyroxine, corticosteroids, oral ntraceptives; diuretics, beta blockers and M.A.O.I.s may affect insulin uirements.
*e and Adverse Effects:* Hypoglycaemia. Local reactions, lipodystrophy hypersensitivity reactions are rarely reported with human insulins.
**rmaceutical Precautions:** Store between 2–8°C, protected from sunlight. lin which has been frozen should not be used.
**l Category:** P **Package Quantities:** 10 ml. glass vials
**NHS Price:** £6.95
**ct Licence Number:** **NORDISK-UK** 3132/0037
**THE WELLCOME FOUNDATION LTD** 0003/0213

Further information is available on request from either Nordisk-UK, Highview House, Tattenham Crescent, Epsom, Surrey KT18 5QJ. Tel. Burgh Heath (07373) 56621 Wellcome Medical Division, The Wellcome Foundation Ltd., Crewe Hall, Crewe, Cheshire, CW1 1UB. Tel. Crewe (0270) 583151.
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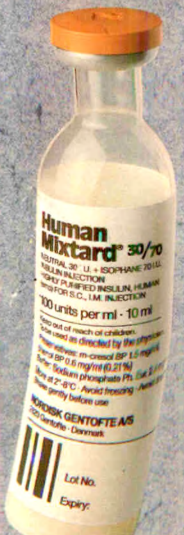

# HUMAN MIXTARD® 30/7

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